National Institute for Health and Care Excellence

Medical technologies evaluation programme

MT417 Axonics sacral neuromodulation system for treating refractory overactive bladder

Consultation comments table

Final guidance MTAC date: 20 March 2020

There were 19 comments from 4 groups:

- 3 company comments
- 2 professional society comments
- 14 comparator company comments

The comments are reproduced in full, arranged in the following groups – (other SNM systems, clinical evidence, economic model, wording changes and consultation question responses).

#	Consultee ID	Role	Section	Comments	NICE response
Other SNM systems					
1	4	Comparator company	General	We ask the Committee to note that a new rechargeable InterStim SNM system; InterStim™ Micro SureScan™ MRI System for Sacral Neuromodulation Therapy has had regulatory approval and is now in use in NHS England. The InterStim™ Micro rechargeable SNM system has similar costs, superior battery consistency and similar, full body MRI compatibility to the Axonics SNM system and is almost 50% smaller than the Axonics device. Medtronic, Inc. filed a lawsuit in November 2019 in the United States District Court for the Central District of California, seeking injunctive relief and damages for infringement against Axonics Modulation Technologies, Inc. (“Axonics”) alleging infringement of patents related to Medtronic’s minimally invasive sacral neuromodulation lead placement procedure and implant	Thank you for your comment. NICE medical technologies guidance evaluates a single medical technology based on the claimed advantages of introducing the specific technology compared with current

				recharging technologies. This serves to illustrate the close similarities, if not identical properties, of the value being claimed by Axonics and the InterStim™ Micro SNM rechargeable device, therefore we ask the Committee to consider that, in the face of overwhelming similarity and limited objective evidence, any guidance produced on the Axonics technology, should only be made if considered and extended to the wider products that are available. The proposed savings as recommended in this draft guidance are clearly not unique compared to other products currently available in the NHS, that are not included in this review. No evidence been provided, either directly or indirectly, for head to head comparison with similar technologies as defined in the scope, therefore the estimated savings cannot be claimed uniquely for Axonics Whilst accepting that clinical evidence on technologies, is often limited, especially comparative evidence with appropriate alternative treatments, our reading of evidence submitted in support of other guidance such as MTG has Senza MT330 Senza spinal cord stimulation (SCS) system for delivering HF10 therapy to treat chronic neuropathic painpain and MTG 33 ENDURALIFE powered CRT-D devices for treating heart failure, show that these head to head comparisons can be done. We ask the Committee to consider the EAC conclusion regarding the limited evidence versus other SNM systems. We suggest that this level of evidence is below the level expected to support production of NICE guidance on this single technology. We suggest that this guidance development process be paused to assess if this is still the correct route for assessment, as the Axonics claims are no longer unique in the marketplace. If the decision is made to proceed with the development of this Medical Technology Guidance for Axonics SNM system, we ask the comparator for the economic assessment is changed to include InterStim™ Micro rechargeable SNM system and that further economic analysis is conducted by the EAC.	management of the condition. We cannot therefore add a new product to a partly completed evaluation, which in any event might well not be fair either to the product originally being evaluated or to the product that is new to the market. It is not a multiple technology assessment and does not compare evidence for all similar technologies in a broader class. These principles are described in further detail in the medical technologies evaluation programme methods guide, and in the block of text at the beginning of the medical technology guidance. This text states that the case for adoption is based on claimed advantages of introducing the specific technology compared with current management of the condition. We consider this to mean the current management of the condition at the

					time the evaluation began, because that is when the evidence search is undertaken. It also states that the specific recommendations in the medical technologies guidance on individual technologies are not intended to limit use of other relevant technologies which may offer similar advantages. A literature search (involving Cochrane, Medline, Embase, PubMed, Scopus and Web of Science) was conducted by the EAC on 18 March 2020. No studies concerning InterStim Micro SureScan MRI System for Sacral Neuromodulation Therapy were identified. Section 4.1 of the guidance describes the committee's discussion around whether InterStim Micro system should be included as a comparator to Axonics SNM system.
2	4	Comparator	1.2	Draft Guidance, page 2: 1.2: states that "the Axonics SNM system "does not need to be	Thank you for your

		company		removed for MRI, so it may be useful …. when a full body MRI is likely” • New InterStim™ SureScan™ MRI leads allow for full body MRI access in both 1.5T and 3T MRI systems, for both the new rechargeable InterStim™ Micro system and with the existing recharge-free InterStim™ II system. The rechargeable system is recharged using a new wireless recharger platform that includes application software that allows the patient to check the recharge status and control the recharge speed as desired. • We ask the committee to note that both the rechargeable and the non-rechargeable InterStim systems are now CE marked for full-body 1.5T and 3T MRI. We ask that this statement is updated to say that there is no difference in the MRI compatibility of all available SNM devices • We ask the Committee to note that the Axonics SNM system has a requirement to run an impedance check prior to MRI imaging. This means that an SNM-trained physician or company rep needs to be in attendance for the MRI. An impedance check is not a requirement for InterStim II non-rechargeable system nor the InterStim Micro rechargeable system which may provide some system benefits versus Axonics. Draft Guidance, page 2: 1.2: states that “the Axonics SNM system is “small …. so, it may be useful for people with a low body mass index (BMI)”. • We ask the Committee to note that the other rechargeable device, InterStimTM Micro device, is 49% smaller than the Axonics device and may also be useful for people with a low BMI. We ask that this statement is updated to say that both rechargeable SNM systems have smaller device footprint than the non-rechargeable system and that InterStimTM Micro is the smallest (this is also relevant to statement in page 3, para 2).	comment. Recommendation 1.2 refers to the clinical benefits of using Axonics SNM system and does not make any reference to the comparator. With regards to inclusion of the new device and MRI compatible leads, please see response to comment 1. The clinical experts stated that an impedance check and the presence of a SNM expert will likely always be required. This is because there will be different devices in use and it would not make sense to leave the patient responsible for knowing if their implant is compatible and checking it is switched off. The committee did not make any changes.
3	4	Comparator company	4.5	Section 4.5: states that: Axonics SNM system has advantages for people with low body mass index or who are likely to need an MRI scan. The clinical experts said that the smaller size of the Axonics SNM system compared with the non-rechargeable device makes it more suitable for people with low body mass index. The full body MRI compatibility of the device means that people with overactive bladder who may need future MRI scanning do not need to	Thank you for your comment. Please see response to comments 1 and 2.

				have their device removed, avoiding replacement surgery. • We ask the committee to note that both the rechargeable and the non-rechargeable InterStim systems are now CE marked for full-body 1.5T and 3T MRI. We ask that this statement is updated to say that there is no difference in the MRI compatibility of all available SNM devices (this is also relevant to statement in page 3, para 2). • We ask the Committee to note that the Axonics SNM system has a requirement to run an impedance check prior to MRI imaging. This means that an SNM-trained physician or company rep needs to be in attendance for the MRI. An impedance check is not a requirement for InterStim II non-rechargeable system nor the InterStim Micro rechargeable system. • We ask the Committee to note that the other rechargeable device, InterStimTM Micro device, is 49% smaller than the Axonics device and may also be useful for people with a low BMI. We ask that this statement is updated to say that both rechargeable SNM systems have smaller device footprint than the non-rechargeable system and that InterStimTM Micro is the smallest (this is also relevant to statement in page 3, para 2).	
Clinical evidence					
4	4	Comparator company	1.1	Draft Guidance Recommendations- Section 1 Page 2: 1.1: states that “Evidence supports the case for adopting Axonics sacral neuromodulation (SNM) system for treating refractory overactive bladder in the NHS”. The MTEP Methods guide states that “The committee needs to be confident that the evidence is of sufficient quality, quantity and consistency to form the basis of robust recommendations”. We ask the Committee to note that no evidence been provided, either directly or indirectly, for head to head comparison with similar technologies as defined in the scope. Whilst accepting that clinical evidence on technologies, is often limited, especially comparative evidence with appropriate alternative treatments, our reading of evidence submitted in support of other guidance such as MTG has Senza MT330 Senza spinal cord stimulation (SCS) system for delivering HF10 therapy to treat chronic neuropathic pain and MTG 33 ENDURALIFE powered CRT-D devices for treating heart failure, shows that these head to head comparisons can be done. We ask the Committee to consider the EAC conclusion regarding the limited evidence versus other SNM systems. We suggest that this level of evidence is below the level expected to support production of NICE guidance on this single technology.	Thank you for your comment. Please see response to comments 1 and 2. The characteristics of medical technologies (section 2.3 of medical technologies evaluation programme process and methods guide) mean that the evidence presented to the committee about their claimed benefits may be associated with a large degree of uncertainty. This has been stated in section 3.1 of the MTG. The

				We ask the Committee to note that the comparator in the decision problem is “other sacral neuromodulation systems” and that Axonics has no evidence comparing Axonics SNM system with other sacral neuromodulation systems, nor do they have any comparator evidence versus conventional medical management, therefore claims of efficacy versus the comparator in the scope or conventional medical management cannot be substantiated. The EAC report concluded that the main limitation of Sponsor’s specific clinical evidence (the ARTISAN-SNM study and the RELAX-OAB study) is that these studies were not randomized controlled studies and do not provide direct comparison between the Sponsor’s technology and the comparator. Both studies were non-comparative, before and after, intra-patient, observational studies reporting patient outcomes as a change from baseline and the EAC concluded that both studies had design and reporting weakness. The EAC report highlighted that neither study was carried out exclusively in a UK setting and findings may not be generalisable to the UK NHS population. They noted that McCrery et al. (2019) reported 40 of 129 people (31%) were “taking a concomitant medication to treat the condition” at baseline. This is not typical of a refractory OAB population in the UK and the EAC report stated that the use of concomitant medication could produce an adjuvant effect of improving overall effectiveness. The EAC concluded that “in the OAB population the published clinical evidence alone may not be sufficient to support a case for adoption of rechargeable SNM devices as an alternative to NHS standard care (non-rechargeable SNM devices). This is primarily because of weaknesses in the published studies, notably the absence of both long-term evidence and robust comparison of devices. The main value proposition of the rechargeable device is that the longer battery life is expected to require fewer surgical procedures; it has not yet been possible to demonstrate these clinical outcomes”. The availability of another rechargeable SNM system which has all of the claimed benefits of the Axonics SNM system and therefore the Axonics claims are no longer unique in the marketplace and there are there are no additional clinical or cost benefits to the healthcare system from using the Axonics system compared with InterStim Micro rechargeable system. We suggest that the Axonics system no longer meets the criteria for development of Medical Technology Guidance as defined in the NICE MTEP Methods.	committee also considered the opinion of expert advisers who gave advice at the committee meeting. The committee added more detail to the ‘further research’ section (section 4.17 in the MTG) to help identify the gaps in the evidence.
5	4	Comparator company	3.2	Section 3.2: states that “RELAX-OAB …… had a follow up of 2 years”. We ask that this statement be clarified to indicate that the 2-year data has not been published in a peer reviewed journal (see page 24 of supporting materials). Section 3.2: states that “RELAX-OAB defined test responders as people whose symptoms responded to therapy at 2 weeks or 1 month after implant”.	Thank you for your comment. Please note this study was published in April 2020, Blok et al. 2020.

				We ask the committee to note that in the 3 month Relax-OAB publication test responders were defined at 1 month.	The committee noted that the statement in section 3.2 refers to all publications of RELAX-OAB and decided no change was necessary.
6	4	Comparator company	3.3, 3.4	Section 3.3., bullet 1: states “mean daily urinary urge incontinence (episodes of urinary leaks) from …..to 1.3±0.3 after 6 months, and 1.4±0.2 at 1 year (p<0.0001)” We ask the committee to note that in the reported data the standard deviation after 6 months is 0.2 instead of 0.3 We ask the committee to make it clear in this paragraph that the 1-year data reported here has not been published in a peer reviewed journal. Section 3.3, bullet 3: states “mean daily urinary urge incontinence (episodes of urinary leaks) from 8.3±0.8 at baseline to 1.8±0.5 after 1 year and to 1.7±0.5 at 2 years (p<0.0001) We ask the committee to note that in the reported data the p value is <0.001 not <0.0001. We ask the committee to make it clear in this paragraph that the 2 years data reported here has not been published in a peer reviewed journal. Section 3.3, bullet 4 states: “urinary frequency episodes (average voids per day) from 14.3±1.1 at baseline to 8.0±0.5 by 1 year and 7.3±0.4 at 2 years (p<0.0001)”. We ask the committee to note that in the reported data the p value is <0.001 not <0.0001. We ask the committee to make it clear in this paragraph that the 2 years data reported here is unpublished. Section 3.3, bullet 4 states: The clinical effectiveness of Axonics sacral neuromodulation (SNM) system was not assessed beyond 2 years. We ask the committee to make it clear in this paragraph that there is no peer-reviewed published data available beyond 12 months. Section 3.4 states: “Both studies reported scores for the domains of the quality-of-life measure ICIQ-OABqol before and after treatment. ARTISAN-SNM reported an average score	Thank you for your comment. The committee heard advice from the external assessment centre and made the following changes to the text: Section 3.3, bullet 1 - mean daily urinary urge incontinence (episodes of urinary leaks) from 5.6±0.3 at baseline to 1.3±0.2 after 6 months, and 1.4±0.3 at 1 year (p<0.0001) Section 3.3, bullet 3 - “mean daily urinary urge incontinence (episodes of urinary leaks) from 8.3±0.8 at baseline to 1.8±0.5 after 1 year (p<0.001) and to 1.7±0.5 at 2 years (p<0.0001)” Section 3.3, bullet 4 - “urinary frequency episodes (average

				improvement of 34 at 1 year and RELAX-OAB reported an average improvement of 29 at 2 years. Absolute before and after quality-of-life scores were not reported". We ask the committee to make it clear in this paragraph that these data have not been published in a peer reviewed journal.	voids per day) from 14.3±1.1 at baseline to 8.0±0.5 by 1 year ($p<0.001$) and 7.3±0.4 at 2 years ($p<0.0001$)". Two-year results from the RELAX-OAB study were published in April 2020. The committee did not make any further changes to the document.
7	4	Comparator company	4.1	Section 4.1 states: "Axonics SNM system improves symptoms and quality of life compared with the standard non-rechargeable system". We ask the Committee to note that there is no comparator evidence to support this statement that the Axonics SNM system improved quality of life more than the non-rechargeable system. The quality of life data is limited to Axonics intra patient, observational studies in a different patient population than the typical refractory OAB population in the UK.	Thank you for your comment. Section 4.1 reports clinical expert opinion and experience and was not intended to comment on the published evidence. The committee did not make any changes.
Economic model					
8	4	Comparator company	1.3	Draft Guidance, page 2: 1.3 states that "Cost modelling suggests that, over 15 years, Axonics SNM system is cost saving compared with the non-rechargeable system by about £6,200 per person. Cost savings are estimated to begin 6 years after implant. This is because the device needs to be replaced less frequently than the non-rechargeable system, assuming Axonics has a life span of at least 15 years". • The base case assumption of a 4.4 year battery life for InterStimTM II is out of date and several publications have reported real world battery longevity of InterStim II of 4.8-6.3 years(1-2V, 14Hz, 210uS, bipolar electrode config, and continuous stim) .1-4 We ask that the base case longevity for InterSimTM II is increased to reflect this estimate and that this new base case is incorporated in the economic model. • The cost modelling suggested savings are based on a comparison between Axonics rechargeable SNM system compared with the non-rechargeable system. We ask this analysis is updated to include a comparison between Axonics SNM system and the newly available InterStimTM Micro rechargeable system. Testing of InterStimTM Micro rechargeable system data in the economic model will show that Axonics is not cost saving versus this comparator. We ask that this statement is updated to reflect the comparison between the two	Thank you for your comment. Please see response to comment 1 regarding the inclusion of a new technology in the cost modelling. The external assessment centre noted that a scenario has been modelled using a lifespan of 5.9 years, which was reported in Widmann

				rechargeable systems. • According to the battery test protocol that was submitted by Axonics and was summarized in the supporting documentation, their battery retains >80% of capacity after 1,000 cycles (based on test of the battery manufacturer Eagle Pitcher). Axonics claims that the battery retains “more than 88%” of initial battery capacity after 1,000 cycles. In contrast, Medtronic has developed the Overdrive battery technology which was first used in our spinal cord stimulation device (Intellis) and is now introduced into Sacral Neuromodulation with the InterStim Micro. It has minimal capacity fade and retains 95% capacity after 3300 daily recharge cycles (equivalent to 9 years) (see ref. attached). Based on the typical usage scenario for Sacral Neuromodulation, we expect zero battery fade over the device lifetime of 15 years for the InterStim Micro (under standard patient therapy settings and implant depth). Furthermore, Overdrive battery technology has rapid recharge capabilities (from empty to full in 60 minutes) and is deep discharge tolerant (has the ability to rapidly recharge from a completely discharged device).	et al. (2019). The impact of device lifetimes was investigated using two-way sensitivity analysis in table 15 of the assessment report. The external assessment centre also noted that the references in the comment Wildmann et al. 2019 [1] reported lifespan for InterStim II as 5.9 years (median), Duchalais et al. 2016 [2] a minimal lifespan of 2.5 years (median not reached), Siegel et al. 2018 [3] did not report device lifespan and Altomare 2009 [4] only included InterStim I, which is no longer available. Although Zhe was referenced in the consultation comment, Altomare 2009 was the study linked by the reference hyperlink [4]. The committee heard from the clinical experts that 4.4 years was an appropriate estimate based on their clinical experience. This is described in section 4.14 of the guidance.

9	4	Comparator company	2.5	The guidance document states that the Axonics SNM device costs £9,660 for the permanent implant. We ask the Committee to note that, based on table 9 of the EAC report and description of device costs in Appendix F, this cost should be £10,160 so either the TL introducer kit or the patient remote has not been included in this total. We ask the Committee to note that the acquisition cost of the clinician programmer for the respective systems has not been considered anywhere in the economic analysis. This is a significant omission as there is a large difference between the cost of the Axonics clinician programmer and the clinician programmer for the non-rechargeable system, with Axonics costing over £6,000 and InterStim II clinician programmer costing £698. This could have significant cost implications for the NHS as currently around 40 implanting centres use at least one programmer. with some needing more to cover outpatients and theatre in urology and colorectal services. Assuming the purchase on one programmer per centre for 40 centres the cost to the NHS for Axonics programmers would be £240,000 compared with £28,000 for the non- rechargeable comparator. It is considered good practice for economic evaluation that all costs associated with the technology be included irrespective of any commercial model that might be in place at a given point in time and we ask that this cost is included in the economic evaluation.	Thank you for your comment. The external assessment centre noted that the patient remote is not included in this figure for either device. This is due to the configuration of the submitted model, however inclusion of the patient remote would be more appropriate. The cost of the remote is included in the overall modelling both at the initial placement and at intervals of 15 years for the non-rechargeable and 7.5 years for the rechargeable device. The device cost at implantation would then be £10,160 for Axonics and £8,483 for the comparator. All calculated results remain unchanged. The clinician programmer is not included in the model. Clinical experts advise that it is normally provided free of charge, however a scenario has been modelled investigating

					the impact of this changing in the future. The impact is small as the device will be used for several patients over a number of years. At the committee meeting the company confirmed that it does not charge for new or replacement clinician programmers and that it has no plans to do so. The committee did not make any changes to the guidance.
10	4	Comparator company	3	Economic Evidence EAC report, page 32, table 5: assumption that there is no difference in SNM therapy effectiveness and discontinuation between rechargeable and non-rechargeable device. based on information for non-rechargeable devices provided in Noblett et al. (2016) for the first year and Chughtai et al. (2015), for all subsequent years The model is based on a previously published model by Noblett et al. (2017) adapted for UK setting however it removes the original assumption that 20% of patients with a rechargeable device will change to non-rechargeable after 4-4.5 years. A 2019 review by Reddy et al found that non rechargeable systems were less likely to be explanted than conventional rechargeable and high-frequency spinal cord stimulation (SCS) systems. Additionally, rechargeable systems were explanted earlier in the devices lifespan as compared to non-rechargeable. This was thought to be possibly related to device “fatigue” with the increased need for maintenance due to charging. A smaller cost-benefit for a rechargeable system would be expected if it is more likely to be explanted therefore, we ask that differential explantation rates are tested in the economic model. EAC report, page 32, table 5: The average lifetime of non-rechargeable InterStim device is reported in Noblett et al. (2017) as 4.4 years based on company’s information which are not accessible now. The base case assumption of a 4.4 year battery life for InterStimTM II is out of date and	Thank you for your comment. The external assessment centre noted that the model used explantation rates from the available literature for Axonics. The sensitivity analysis included therapy discontinuation as one of the variables. A scenario has been modelled using a lifespan of 5.9 years, which was reported in Widmann et al. (2019). The infection rates were based on available literature for

				several publications have reported real world battery longevity of InterStim II of 4.8-6.3 years(1-2V, 14Hz, 210uS, bipolar electrode config, and continuous stim) .1-4 We ask that the base case longevity for InterSimTM II is increased to reflect this estimate and that this new base case is incorporated in the economic model. EAC Report, page 35, table 6: Implant site infection, 1st procedure: The sponsor's submitted model assumed there is no difference in infection rates between Axonics and the comparator, based on Brueseke et al 2015. The EAC reduced the rate submitted by the sponsor for Axonics from 4.48% to 1%, based on McCrery et al 2019, whilst the rate has been left at 4.48% for comparator There is no clinical data available (head-to-head comparison or other appropriately designed trial) to show an advantage of a reduced number of implant site infections events for the Axonics device compared with the non-rechargeable comparator. The EAC report highlighted the lack of comparator evidence between the Axonics technology and the comparator and stated that, with no randomised recruitment, there is a risk that variation in patient selection and surgical techniques could have influenced treatment outcomes" The Axonics SNM System uses the same stimulation parameters, has the same nerve target and is implanted through the same surgical procedure as the non-rechargeable comparator; therefore, infection rates would be expected to be similar if controlled for variations in patient selection and surgical technique. As the assumption of different infection rates has not been demonstrated by the available clinical data, we ask that the assumption of no difference in infection rates is used in the model. EAC Report, page 35, table 6: Brueske et al 2015 as source of infection rates and explant rates. We do not consider this a robust source for infection and explant rates as this is a US retrospective analysis, which has a very different patient population from the OAB refractory implanted patients in the UK. Half of the patients were potentially immunosuppressed and there was a change of practice during the study period so there are different infection rates before and after. The proposed 30% of infections requiring I/V antibiotics seems excessively high. Serious infections most often result in explant therefore this is not representative of the UK implanted population. The cost used for these I/V antibiotics is £5,216 based on US costs for infections in implantable cardiac devices and include 10-14 days hospital stay, which again is not representative of UK practice. As infection costs and rates influence the predicted savings in	Axonics and the comparator device. Clinical experts advised that 1% is a realistic infection rate for either device. An additional scenario has been modelled to show the impact of this. The cost of antibiotics was based on an NHS reference cost WH07B Infections or Other Complications of Procedures, with Multiple Interventions, with CC Score 0-1, Non-elective surgery. This has not been investigated further, and any change would have a minimal impact on the model outcomes. Clinical experts advised that smaller devices are less likely to cause discomfort. The external assessment centre base case remains unchanged, however the impact of pain parameters is investigated in an additional scenario. The adverse events of

				the draft guidance, we ask that a more suitable references are found that more accurately reflects UK infection costs relating to SNM implants. EAC Report, page 36, table 6: assumptions re implant site pain. The EAC reduced the rate submitted by the sponsor for the Axonics system from 4.04% to 2%, based on McCrery et al 2019, whilst the rate has been left at 4.04% for comparator There is no clinical data available (head-to-head comparison or other appropriately designed trial) to show an advantage of a reduced number of implant site pain events for the Axonics device compared with the non-rechargeable comparator. Pain will depend on patient population (BMI), implant location, physician skill etc. and although a smaller device has potential advantages regarding pain this has not been proven in comparator studies. The EAC report highlighted the lack of comparator evidence between the Axonics technology and the comparator and stated that, with no randomised recruitment, there is a risk that variation in patient selection and surgical techniques could have influenced treatment outcomes" As the assumption of different infection rates has not been demonstrated by the available clinical data, we ask that the assumption of no difference in pain event rates is used in the model. EAC report, page 46, table 12: summary of base case results In table 12 there are more adverse events for the comparator, as would be expected however given that the Axonics device and lead are more expensive (and the fact that some events lead to replacement of the entire system), we would expect the cost of adverse events to be quite similar between the groups (since quite a lot of the adverse events lead to replacement of at least some device components). It is unclear In Table 12 why the adverse event costs are quite a bit higher for InterStim II (£1,571) than for Axonics (£1,177). We were unable to replicate the total cost of £19,812 for Axonics reported in Table 12. The actual model has this figure at £19,695 – the discrepancy appears to be in the adverse event costs (the table says £1,177, while the model says £1,060). Economic Model, Results BIM worksheet: Detailed Inputs 1 of 4: Cohort and Device Characteristics- Technology parameters section The base case assumption of a 4.4 year battery life for InterStimTM II is out of date and several publications have reported real world battery longevity of InterStim II of 4.8-6.3	infection and pain are linked to implantation or replacement events. The comparator device has more replacement events and therefore a very slightly higher total cost. Following the fact check, the external assessment centre corrected the use of device components at replacement procedures. This had a very small impact on the model outcome, given other uncertainties. This is presented as an additional scenario in table 12 of the assessment report. As the most current model, this is the one that was made available. There will be slight discrepancies to other tables remain unaltered. The clinician programmer is not included in the model. The company confirmed that this is provided free of charge. The committee discussed the extra

				years(1-2V, 14Hz, 210uS, bipolar electrode config, and continuous stim) .1-4 We ask that the base case longevity for InterSimTM II is increased to reflect this estimate and that this new base case is incorporated in the economic model. Economic Model, Detailed inputs 4 of 4 worksheet: Inpatient implantation of whole SNM system (lead and generator) section The inpatient implant section describes the device cost for InterStim as including lead, introd, IPG and programmer. For Axonics the costs are described as “permanent implant after PNE kit. The cost of £9,660 does not appear to include the patient programmer which is stated as included in the InterStim costs in the table. If the patient programmer is included in the Axonics costs, as per the list of components in Table 9 of the EAC report, we suggest that this device cost for Axonics should be £10,160 and not £9,660. Economic Model, Detailed inputs 4 of 4 worksheet: Infections section Device replacement rates and I/V treatment rates are taken from Brueske 2015. We do not consider this a robust source for infection and explant rates as this is a US retrospective analysis, which has a very different patient population from the OAB refractory implanted patients in the UK. Half of the patients were potentially immunosuppressed and there was a change of practice during the study period so there are different infection rates before and after. The proposed 30% of infections requiring I/V antibiotics seems excessively high. Serious infections most often result in explant therefore this is not representative of the UK implanted population. The cost used for these I/V antibiotics is £5,216 based on US costs for infections in implantable cardiac devices and include 10-14 days hospital stay, which again is not representative of UK practice. As infection costs influence the predicted savings in the draft guidance, we ask that a more suitable reference is found that more accurately reflects UK infection costs relating to SNM implants. Economic Model, Detailed inputs 4 of 4 worksheet: Settings and care Costs section We ask the Committee to note that the acquisition cost of the clinician programmer for the respective systems has not been considered anywhere in the economic analysis. This is a significant omission as there is a large difference between the cost of the Axonics clinician programmer and the clinician programmer for the non-rechargeable system, with Axonics costing over £6,000 and InterStim II clinician programmer costing £698. This could have significant cost implications for the NHS as currently around 40 implanting centres purchase at least one programmer. with some needing more to cover outpatients and theatre in urology and colorectal services. Assuming the purchase on one programmer per centre for 40 centres the cost to the NHS for Axonics programmers would be £240,000 compared with £28,000 for the non- rechargeable comparator. It is considered good practice for economic evaluation that all costs associated with the	work done by the external assessment centre with the clinical experts. It decided that the rate of infection should be the same for both Axonics and the comparator changing the final cost saving to £6,025. This is described in sections 4.12 and 4.13 of the guidance.

				technology be included irrespective of any commercial model that might be in place at a given point in time and we ask that this cost is included in the economic evaluation. Ref 1. Widmann B et al. J Neurogastroenterol Motil. 2019 Jan 31;25(1):159-170. 2. Duchalais et al. Int J Colorectal Dis. 2016 Feb;31(2):439-44. 3. Siegel S et al. Female Pelvic Med Reconstr Surg. 2018 Jul/Aug;24(4):267-271. 4. CuiZhe.https://pdfs.semanticscholar.org/ef17/aa6b02290ced3ac8599de48b6205e735b0df.pdf 5. Lehur P. A., Sørensen M., Dudding T. C. et al. 2020. Programming Algorithms for Sacral Neuromodulation: Clinical Practice & Evidence. Recommendations for Day-to-Day Practice. Neuromodulation 14 January 2020. 6. Reddy R.D., Moheimani R., Yu G.G., Chakravarthy K.V. 2019.A Review of Clinical Data on Salvage Therapy in Spinal Cord Stimulation.Neuromodulation 2019; E-pub ahead of print. DOI:10.1111/ner.13067 7. Schade CM, Sasaki J, Schultz DM, Tamayo N, King G, Johanek LM. Assessment of patient preference for constant voltage and constant current spinal cord stimulation. Neuromodulation. 2010;13(3):210-217. http://dx.doi.org/10.1111/j.1525-1403.2010.00284.x 8. North and Sung North RB, Sung JH. Postural Changes in Spinal Cord Stimulation: Current Versus Voltage Sources. Pain Med. 2011;12(3):517. http://dx.doi.org/10.1111/j.1526-4637.2011.01070.x 9. Washburn S, Catlin R, Bethel K, Canlas B. Patient-perceived differences between constant current and constant voltage spinal cord stimulation systems. Neuromodulation. 2014;17(1):28-36. http://dx.doi.org/10.1111/ner.12085 10. Ooi M, Yanamoto F, Sato H, et al. Constant Current vs. Constant Voltage Systems for Temporal Spinal Cord Stimulation for Intractable Pain. Acta Med Okayama. 2017;71(6):531-537. http://dx.doi.org/10.18926/AMO/55591 11. Ramirez de Noriega F, Eitan R, Marmor O, et al. Constant current versus constant voltage subthalamic nucleus deep brain stimulation in Parkinson's disease. Stereotact Funct Neurosurg. 2015;93(2):114-121. http://dx.doi.org/10.1159/000368443 12. Lettieri C, Rinaldo S, Devigili G, et al. Clinical outcome of deep brain stimulation for dystonia: constant-current or constant-voltage stimulation? A non-randomized study. Eur J Neurol. 2015;22(6):919-926. http://dx.doi.org/10.1111/ene.12515 13. Preda F, Cavandoli C, Lettieri C, et al. Switching from constant voltage to constant current in deep brain stimulation: a multicenter experience of mixed implants for movement disorders. Eur J Neurol. 2016;23(1):190-195. http://dx.doi.org/10.1111/ene.12835 14. Amami P, Mascia MM, Franzini A, Saba F, Albanese A. Shifting from constant-voltage to constant-current in Parkinson’s disease patients with chronic stimulation. Neurological Sciences. 2017;38(8):1505-1508. http://dx.doi.org/10.1007/s10072-017-2961-2	
Wording changes					
11	1	Company	rationale	"The battery is expected to last at least 6 years, at which point Axonics SNM system becomes cost saving to the NHS." We believe that this statement is misleading. It implies that	Thank you for your comment.

				technical data supports a minimum battery life of 6 years for the Axonics system, whereas the technical evaluation confirms that at normal stimulation parameters the device will last at least 15 years per its label. Perhaps this could be changed into "The Axonics SNM system becomes cost saving to the NHS at 6 years, a duration that the device should well exceed given its estimated lifetime."	The committee did not think that it was appropriate make this change to the rationale section as it is intended to be a lay summary of the guidance. The committee decided that section 3.5 was an adequate summary of the technical report.
12	1	Company	3.8	As indicated in the first comment, this wording seems to imply that data supports a minimum life scenario of 6 years for the Axonics system. The 6 years threshold is driven by the economic model only. Perhaps the last sentence could be rephrased as "Threshold analysis showed that Axonics SNM system remains cost saving even with a minimum life span of 6 years."	Thank you for your comment. Section 3.8 has been reworded to state: 'Threshold analysis showed that Axonics SNM system becomes cost saving when the life span of the technology is 6 years or longer.'
13	1	Company	4.1	The Axonics test phase allows for 2 programs and not 1 program. Once the permanent implant has occurred, the Axonics system allows for 1 program only. Perhaps this was not clearly conveyed in the discussion with experts. This should be corrected as it is not in line with the Axonics product manuals.	Thank you for your comment. Section 4.1 has been updated as suggested.
14	4	Comparator company	4.1	Section 4.1 states: Axonics SNM system has 1 program that can be optimised while the standard non-rechargeable SNM system has 4 default programs that a patient can switch across remotely. We ask that this statement be updated to clarify that the standard non-rechargeable system programmes can also be optimised.	Thank you for your comment. Section 4.1 has been updated as suggested.
15	4	Comparator company	4.5, 4.7	Section 4.5: states that: Axonics SNM system has advantages for people with low body mass index or who are likely to need an MRI scan. The clinical experts said that the smaller size of the Axonics SNM system compared with the non-rechargeable device makes it more suitable for people with low body mass index. The full body MRI compatibility of the device means that people with overactive bladder who may need future MRI scanning do not need to have their device removed, avoiding replacement surgery.	Thank you for your comment. Please see the response to comment 1 regarding the inclusion of a new

				• We ask the committee to note that both the rechargeable and the non-rechargeable InterStim systems are now CE marked for full-body 1.5T and 3T MRI. We ask that this statement is updated to say that there is no difference in the MRI compatibility of all available SNM devices (this is also relevant to statement in page 3, para 2). • We ask the Committee to note that the Axonics SNM system has a requirement to run an impedance check prior to MRI imaging. This means that an SNM-trained physician or company rep needs to be in attendance for the MRI. An impedance check is not a requirement for InterStim II non-rechargeable system nor the InterStim Micro rechargeable system. • We ask the Committee to note that the other rechargeable device, InterStimTM Micro device, is 49% smaller than the Axonics device and may also be useful for people with a low BMI. We ask that this statement is updated to say that both rechargeable SNM systems have smaller device footprint than the non-rechargeable system and that InterStimTM Micro is the smallest (this is also relevant to statement in page 3, para 2). Section 4.5 states: This consideration was also relevant to people with chronic conditions such as multiple sclerosis, who are likely to need regular MRI scans. We ask that this statement be updated to clarify that Axonics don't have data for use in people with multiple sclerosis. Section 4.7 states: The committee concluded that Axonics SNM system should be the only treatment for overactive bladder until symptoms are no longer adequately controlled. We suggest that this statement may be misinterpreted as the Axonics system should be the only SNM system to be used. We ask that this statement is rephrased to clarify that it refers to the concomitant use of medication.	comparator device. The consideration regarding people with multiple sclerosis was intended to note a potential reduction in inequality and was not a comment on the evidence. The committee decided to reword section 4.7 to clarify that no other treatments (including medication) should be used alongside Axonics SNM system, unless symptoms are no longer adequately controlled.
16	4	Comparator company	3	Page 9, section 1 of the EAC report: lists one of the innovative aspects of the Axonics technology as: the IPG is designed to operate on constant current, which allows automatic adjustment of stimulation current (amplitude) according to tissue impedance. We ask the Committee to note that the issue of constant current has been addressed in a recent article by the European expert group6 who concluded the following: “At present the InterStim™ system is based on two different energy delivery technologies. Whereas the external test stimulator (Verify™) works with constant current (mA), the InterStim™ II IPG delivers the energy on a constant voltage basis (V). There is no evidence	Thank you for your comment. As this comment refers to the external assessment centres technical report, no change to the guidance was made.

				that one stimulation modality is clinically superior to the other. As long as the impedance is stable both systems deliver the same amount of energy to the sacral nerve. There are no data to suggest that constant current systems require significantly fewer amplitude adjustments than constant voltage systems". Furthermore, there are a number of publications7-14 from other neuromodulation indications (SCS and DBS) that have tried to evaluate potential advantages of either constant current or constant voltage. (add references mentioned below here). Similar to the conclusion of the European expert group all but one (Lettieri et al12) did not find any statistically significant advantages of constant current over constant voltage or vice versa in efficacy outcomes or patient preference.	
Consultation question responses					
17	2	Professional society	General	*Has all of the relevant evidence been taken into account?* Yes, the evidence base appears robust, and includes two main trials (included in chapter 3 Evidence). *Are the summaries of clinical and resource savings reasonable interpretations of the evidence?* Yes *Are the recommendations sound and a suitable basis for guidance to the NHS?* Yes, recommendations and reasons given (with supporting documentation) appear sound. *Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?* NO This is also addressed within the document	Thank you for your comment.
18	3	Professional society	General	Feedback to BSUG on NICE consultation on the Axonic SNM technology The executive summary of the EAC (external assessment centre) report rightly starts with outlining that the evidence for the new technology is derived from two single arm (non-comparative) studies with follow up of 2 years, therefore conceding that with no comparative studies the evidence is poor and the follow up is not long enough to confirm long term effectiveness and safety. This is especially important as the new device only becomes more cost-saving by year 6 of implantation, when compared to the current device used in the NHS. In the supplementary papers, the EAC report acknowledges the assumptions for the economic model and adds further assumptions that there is not difference in the adverse events rate between rechargeable and chargeable SNM devices. However, as the	Thank you for your comment. The committee added more detail to section 4.17 to help identify the gaps in the evidence.

				rechargeable SNM device is based on constant current technology (whilst the chargeable SNM is based on constant voltage technology), this has the potential of leading to less need for re-programming, but at the expense of predicted device life for the rechargeable device. This effect and its size are unknown at the moment, but as the basis of economic advantage of the rechargeable technology is a longer device life, it could have a significant effect on the economic calculations. This is acknowledged in page 14 of the Newcastle EAC report, but not built into the model. Having said that, the sensitivity analysis of the model did show that the claim of 15 year battery life for the new device is robust within reasonable variation of device parameters. Wider variations could change the model considerably though. The economic model has the weakness of comparing post-marketing data of non- chargeable device (from an American database) to company sponsored research data for the chargeable device. On balance, I believe the endorsement of the technology is fair, despite the weak evidence, but this should be done carefully without unjustified enthusiasm and accompanied by strong governance arrangements such as: 1. Audit 2. Mandatory MHRA reporting of device adverse events 3. Mandatory national database entry (BSUG, BAUS) for all operated cases. Additional Comment from the BSUG Exec BSUG Comments on Axonics sacral neuromodulation system for bladder control in people with symptoms of overactive bladder 2.3 Innovative Aspect: the battery life of 15 years that is quoted is for ex vivo studies as the longest duration of in vivo studies is only 2 years. 3.1 Evidence: the two studies on which the recommendations are based have very small numbers and are not comparative studies. Follow up is also relatively short at 2 years.	
19	4	Comparator company	General	*Has all of the relevant evidence been taken into account?* Yes *Are the summaries of clinical and resource savings reasonable interpretations of the evidence?* We do not agree that the evidence supports the case for adopting Axonics sacral neuromodulation (SNM) system for treating refractory overactive bladder in the NHS. No evidence been provided, either directly or indirectly, for head to head comparison with similar technologies as defined in the scope. The EAC concluded that there was limited evidence versus other SNM systems. We suggest that this level of evidence is below the level expected to support production of NICE guidance on this single technology	Thank you for your comment. Please see the response to comment 1.

				Are the recommendations sound and a suitable basis for guidance to the NHS? We do not believe that the recommendations are sound and a suitable basis for guidance to the NHS due to the lack of comparator evidence as defined in the scope and the availability of another rechargeable device which has close similarity in terms of clinical benefits and resource savings to the NHS. We beleive therefore that any guidance produced on the Axonics technology, should only be made if considered and extended to the wider products that are available. The proposed savings as recommended in this draft guidance are clearly not unique compared to other products currently available in the NHS, that are not included in this review. No evidence been provided, either directly or indirectly, for head to head comparison with similar technologies as defined in the scope, therefore the estimated savings cannot be claimed uniquely for Axonics Whilst accepting that clinical evidence on technologies, is often limited, especially comparative evidence with appropriate alternative treatments, our reading of evidence submitted in support of other guidance such as MTG has Senza MT330 Senza spinal cord stimulation (SCS) system for delivering HF10 therapy to treat chronic neuropathic pain and MTG 33 ENDURALIFE powered CRT-D devices for treating heart failure, shows that these head to head comparisons can be done. We ask the Committee to consider the EAC conclusion regarding the limited evidence versus other SNM systems. We suggest that this level of evidence is below the level expected to support production of NICE guidance on this single technology. We suggest that this guidance development process be paused to assess if this is still the correct route for assessment, as the Axonics claims are no longer unique in the marketplace. If the decision is made to proceed with the development of this Medical Technology Guidance for Axonics SNM system, we ask the comparator for the economic assessment is changed to include InterStim™ Micro rechargeable SNM system and that further economic analysis is conducted by the EAC. *Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?* No	

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