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Medical technology consultation: MT417 Axonics

Supporting documentation – Committee papers

The enclosed documents were considered by the NICE medical technologies advisory committee (MTAC) when making their draft recommendations:

1. **EAC assessment report** – an independent report produced by an external assessment centre who have reviewed and critiqued the available evidence.
2. **Assessment report overview** – an overview produced by the NICE technical lead which highlights the key issues and uncertainties in the company's submission and assessment report.
3. **Scope of evaluation** – the framework for assessing the technology, taking into account how it works, its comparator(s), the relevant patient population(s), and its effect on clinical and system outcomes. The scope is based on the sponsor's case for adoption.
4. **Adoption scoping report** – produced by the adoption team at NICE to provide a summary of levers and barriers to adoption of the technology within the NHS in England.
5. **Sponsor submission of evidence** – the evidence submitted to NICE by the notifying company.
6. **Expert and patient questionnaires** – expert commentary gathered by the NICE team on the technology.
7. **EAC correspondence log** – a log of all correspondence between the external assessment centre (EAC) and the company and/or experts during the course of the development of the assessment report.
8. **Company fact check comments** – the manufacturer's response following a factual accuracy check of the assessment report.

Please use the above links and bookmarks included in this PDF file to navigate to each of the above documents.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

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

External Assessment Centre report

Produced by:	**Cedar**
Authors:	**Ruth Louise Poole, Senior Researcher** **Megan Dale, Senior Researcher/Health Economist** **Dr Helen Morgan, Senior Information Specialist and Systematic Reviewer** **Edyta Ryczek, Researcher** **Brett Cohen, Health Informatics Trainee, Cardiff & Vale University Health Board** **Professor Grace Carolan-Rees, Director**
Correspondence to:	**Cedar Healthcare Technology Research Centre** **Cardiff and Vale University Health Board** **Cardiff Medicentre** **Heath Park, CARDIFF CF14 4UJ**
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Contains confidential information	Yes
Number of attached appendices	7

Purpose of the assessment report

The purpose of this External Assessment Centre (EAC) report is to review and critically evaluate the company's clinical and economic evidence presented in the submission to support their case for adoption in the NHS. The report may also include additional analysis of the submitted evidence or new clinical and/or economic evidence. NICE has commissioned this work and provided the template for the report. The report forms part of the papers considered by the Medical Technologies Advisory Committee when it is making decisions about the guidance

Declared interests of the authors

None

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Rider on responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Contents

ABBREVIATIONS

Term	Definition
AE	Adverse event
ARTISAN-SNM	Axonics SacRal NeuromodulaTIon System for Urinary Urgency Incontinence TreatmeNt (study title)
AUGS	American Urogynecologic Society
CASP	Critical Appraisal Skills Programme
CI	Confidence Intervals
EAC	External Assessment Centre
ICER	Incremental Cost Effectiveness Ratio
ICIQ-OABqol	Institut Català d'Investigació Química overactive bladder quality of life (questionnaire)
IPG	Implantable Pulse Generator
ITT	Intention to Treat
IUGA	International Urogynecological Association
MCID	Minimal Clinically Important Difference
MHRA	Medicines & Healthcare products Regulatory Agency
MTEP	Medical Technologies Evaluation Programme
NA	Not applicable
NICE	National Institute for Health and Care Excellence
OAB	Overactive bladder
PNE	Percutaneous Nerve Evaluation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
RELAX-OAB	Treatment of REfractory Overactive BLadder with the AXonics Sacral Neuromodulation System (study title)
SCS	Spinal cord stimulation
SE	Standard error
SNM	Sacral neuromodulation
TL	Tined lead
UF	Urinary frequency
UI	Urinary incontinence
UTI	Urinary tract infection
UUI	Urge urinary incontinence *or* Urgency urinary incontinence

Executive Summary

All clinical evidence relating to the Axonics technology originates from 2 single-arm studies, both relevant to the scope in regard to population, intervention and outcome measures. The same publications were identified by the company and the EAC. Limitations of both study designs and reporting are indicative of low quality evidence, and the EAC was not able to assess comparative effectiveness against alternative SNM systems. Follow-up is limited to a maximum of 2 years, so it has not been possible to verify long-term safety or clinical effectiveness.

Comparisons between baseline measures and follow-up up to 1 year (ARTISAN-SNM study) and 2 years (RELAX-OAB) show reductions in symptoms of UUI and UF, and improvements in condition-specific quality of life. Subjective assessments suggest that patients are satisfied with treatment, and that the frequency and duration of battery recharging is acceptable. No serious device-related adverse events were reported. The majority of AEs were reported early as a result of stimulation discomfort, which was resolved with reprogramming. There were low numbers of device explantations and procedure-related wound infections.

The economic model compares the Axonics device with a non-rechargeable comparator, with a 15 year time horizon. The model assumes that both devices sit at the same point in the UK NHS clinical pathway, and that they both have equal clinical effectiveness. Given this assumption, the use of Axonics rechargeable device remained cost saving when compared to a non-rechargeable device, despite several EAC amendments and sensitivity testing. The model is strongly driven by the expected device lifetimes and device costs. The Axonics device is slightly more expensive than the non-rechargeable comparator, but this is offset by the longer expected lifetime of the rechargeable device.

The EAC considers that the clinical and economic evidence supports the case for adoption of the technology.

Decision problem

The company have not proposed any variation to the decision problem specified in the scope.

Decision problem	Scope	EAC comment
Population	People with symptoms of overactive bladder for whom conservative therapy and drug treatment have failed or are not suitable	
Intervention	Axonics Sacral Neuromodulation System	
Comparator(s)	Other sacral neuromodulation systems	
Outcomes	The outcome measures to consider include: Primary outcomes • Responder rate (% of patients who experience 50% or more reduction in their leaks compared to baseline) • Level of reduction in overactive bladder symptoms such as average daily number of urgency leaks • The number of surgical interventions to replace SNM devices and the risks associated with these procedures • Time to battery depletion • Ease of use of device • Procedure related infection rates • Incidence of therapeutic failure • Improvement in quality of life including pain and discomfort Secondary outcomes • Explantation rate due to MRI • Time to revision surgery • Level of patient and carer satisfaction • Device-related adverse events	

1 Overview of the technology

The Axonics sacral neuromodulation (SNM) system (Axonics Modulation Technologies, Inc.), is intended for use in treating the symptoms of overactive bladder, specifically in people for whom conservative therapy and drug treatment have failed or are not suitable. It delivers sacral nerve stimulation therapy through an implantable pulse generator (IPG) stimulator implanted subcutaneously in the upper buttock.

A handheld remote control activates the stimulator, adjusts the stimulation amplitude, and checks the battery status. Lead electrodes implanted through corresponding sacral foramen transmit electrical pulses from the stimulator to the S3 or S4 sacral nerve that controls the bladder. The implanted device is programmed by a clinician in an outpatient setting using a portable tablet.

The stimulator is powered by a rechargeable battery. A wireless charger, attachable to the skin over the implanted stimulator, is used to charge the stimulator. It is recommended that the battery is recharged at home by the user every 1-2 weeks, for 30 minutes to 1 hour.

Specialised urologists or urogynaecologists carry out the procedure as a day case. Before committing to a permanent implantation, the technology is trialled for a few weeks to evaluate the efficacy of therapy in improving symptoms (the therapeutic response). The trial involves inserting a thin temporary wire near the sacral nerves, which is connected to an external stimulator. A 3-day bladder diary is completed by the user before and after the procedure to assess improvement in symptoms. People who report at least a 50% improvement in symptoms during the trial are eligible to undergo permanent implantation procedure.

Innovative aspects of the Axonics technology are:

- the stimulator is powered by a rechargeable battery with an expected life span of at least 15 years (comparator non-rechargeable SNM devices are explanted and replaced every 4-5 years)
- the IPG is compatible with full-body MRI (existing non-rechargeable SNM devices must be explanted)
- the IPG is smaller than existing non-rechargeable SNM devices
- the IPG is designed to operate on constant current, which allows automatic adjustment of stimulation current (amplitude) according to tissue impedance.

The Axonics SNM system received a CE mark as a class III medical device in June 2016 for the treatment of overactive bladder, faecal incontinence and urinary retention. Faecal incontinence and urinary retention are beyond the remit of this assessment.

2 Clinical context

NICE's guidelines on urinary incontinence and pelvic organ prolapse in women and lower urinary tract symptoms in men recommend initial management of symptoms with conservative methods (such as lifestyle interventions, behavioural techniques and physical therapies) or drug treatment. When conservative methods and drug treatment fail, investigation to assess detrusor overactivity is recommended. If detrusor overactivity exists, botulinum toxin type A can be injected into the bladder wall. The use of botulinum injection may be associated with a need for clean intermittent catherisation or the use of temporary indwelling catheters.

If a patient is unwilling to accept the possible risk of catherisation with botulinum injection or if botulinum injection fails, the NICE guideline on urinary incontinence and pelvic organ prolapse in women recommends that percutaneous sacral nerve stimulation should be offered. NICE's interventional procedures guidance on sacral nerve stimulation for urge incontinence and urgency-frequency suggests SNM as an option for people who have not responded to conservative management or drug treatment. Alternative invasive treatment options include irreversible bladder reconstruction (augmentation cytoplasty) and urinary diversion.

Expert advisers have confirmed that options for managing OAB syndrome in the UK NHS are accurately reflected by the following summary (Marcelissen et al. 2018):

- First-line: behavioural (such as bladder training)
- Second-line: pharmacotherapy
- Third-line: minimally-invasive therapies (botulinum toxin, percutaneous tibial nerve stimulation – PTNS, or SNM), or surgical procedures (such as augmentation cystoplasty or urinary diversion).

Only one other SNM system is currently commercially available in the UK for the management of symptoms of OAB. The InterStim SNM IPG (and its successor InterStim II) is a non-rechargeable device and considered to be standard care in the UK NHS. It is incompatible with full-body MRI scans; if a patient is likely to require a scan in the future, the SNM device would either not be implanted, or would need to be explanted prior to undergoing an MRI scan.

The EAC believes that the company's description of the current clinical context is appropriate and relevant to the decision problem under consideration. Expert advisers have confirmed that introduction of the Axonics SNM system (as an alternative to the non-rechargeable system) would not require a change to the pathway.

Special considerations, including issues related to equality

The NICE equality impact assessment identifies that urinary incontinence is associated with the protected characteristics of age, disability, sex and pregnancy. The Axonics system is contraindicated in people who cannot operate the device, which could include people with physical or cognitive impairment.

The EAC did not identify any additional equalities issues.

3 Clinical evidence selection

3.1 Evidence search strategy and study selection

The EAC consider that the company's search strategy was weak and lacked defined medical subject headings. The search approach was very limited with only one database being searched; details are provided in Appendix A. Therefore, to ensure that all relevant evidence had been identified, the EAC conducted their own systematic search, to include periods from 1st January 2010 until 21st August 2019. Ten bibliographic databases and 2 clinical trial registries were searched using a range of free text terms and (where appropriate) subject headings. The MHRA's medical device alerts and field safety notices were searched for adverse events. Details are provided in Appendix A. The new search conducted by the EAC did not lead to the identification of additional studies or publications relevant to the scope.

The company included clinical evidence on the Axonics rechargeable sacral neuromodulation technology, as well as evidence on other sacral neuromodulation systems. Single-arm evidence relating to the non-rechargeable InterStim (Medtronic) device was provided. The scope published by NICE states that the intervention is the Axonics sacral neuromodulation system; the EAC excluded any evidence where the Axonics system was absent from either treatment or comparator groups.

Table 1: Studies selected by the EAC as the evidence base.

For each of the ‘design’, ‘participants’ and ‘outcomes’ entries colour coding indicates whether the study matches the scope fully, partially, or not at all: 

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC Comments
McCrery (2019) Lane (2020), unpublished abstract. ARTISAN-SNM study US and Europe (The Netherlands, Belgium, France and UK)	Before and After study Participants implanted with tined lead and Axonics IPG in a single, non-staged procedure, without requiring prior testing with an external trial system. Funded by Axonics Modulation Technologies, Inc. Status of study: 6 months results published in embargo version only (at time of writing) (McCrery 2019); 12 months results unpublished abstract submitted to AUGS/IUGA 2020 Scientific Meeting (Lane 2020) intervention ● comparator ●	n = 129 with urinary urge incontinence n = 127 female; n = 2 male Average age (years): mean = 59.3, range = 21-86 19 centres ●	All outcomes were compared to baseline. **Primary outcome measure:** Therapy responder rate (defined as ≥ 50% reduction in UUI episodes) at 6 months **Secondary outcomes:** Change in number of overactive bladder symptoms such as UUI episodes (leaks), urinary frequency (voids) Change in Quality of life (ICIQ-OABqol score) Patient satisfaction Ease and frequency of battery charging; acceptability of recharging experience. Adverse events Number of explantations (with reasons) ●	The study design is a 'before and after' study therefore there is no separate comparator arm. Company funded study.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC Comments
Blok (2018a) Blok (2018b) Blok (2019a) Blok (2019c), unpublished manuscript. RELAX-OAB study Europe (The Netherlands, Belgium, France and UK)	Before and After study Participants implanted with tined lead and Axonics R-SNM in a single, non-staged procedure, without requiring prior testing with an external trial system. Funded by Axonics Modulation Technologies, Inc. Status of study: 3 and 12 month results published. Unpublished 2 year results provided by company. intervention ● comparator ●	n = 51 (n = 50 with urinary frequency, n = 37 with urinary incontinence) n = 38 female; n = 13 male Average age (years): mean = 51, range = 21-77 7 centres ●	All outcomes were compared to baseline. **Primary outcome measure:** Mean change in ICIQ-OABqol HRQoL total score at 3 months, compared to baseline. **Secondary outcomes:** Responder rate (defined as ≥50% reduction in urinary incontinence episodes per day or voids per day or reduction to <8 voids per day). Change in Quality of life (ICIQ-OABqol score; ICIQ-UI Short Form) Patient satisfaction Adverse events Number of explantations (with reasons) ●	The study design is a 'before and after' study therefore there is no separate comparator arm. Company funded study.

4 Clinical evidence review

4.1 Overview of methodologies of all included studies

Two studies (ARTISAN-SNM and RELAX-OAB) were consistent with the scope of this assessment, and were both observational in design. These studies lack direct comparators, reporting instead intra-patient before-and-after changes in outcome measures, with follow-up limited to 2 years. Although the studies have some sites and authors in common, recruitment periods did not coincide; the company has confirmed that no patient would have been included in both studies.

The main differences in design were the primary outcome measure, and the study population. Differences in populations are reflected in criteria for defining "response to therapy" (table 2). All indications are relevant to the scope.

Table 2. Definition of 'response to therapy' in study subgroups.

Study	Population definition	Definition of 'response to therapy'	Definition of Test Responder	Time between baseline and therapy response measurement
ARTISAN-SNM	Urinary urgency incontinence	≥50% reduction in UUI episodes per day	People who were therapy responders at 1 month	Primary outcome measure at 6 months
RELAX-OAB	Overactive bladder (urinary urge incontinence with or without urinary frequency) ≥8 voids per day and/or ≥2 incontinence episodes over 72 hours	**Urinary incontinence therapy response:** ≥50% reduction in leaks (urinary incontinence episodes) *or* **Urinary frequency therapy response:** ≥50% reduction in voids *or* reduction to <8 voids per day	People who were therapy responders at the 2-week or 1-month follow-up visit	Secondary outcome measured at 3 months, 6 months, 1 year and 2 years

4.2 Critical appraisal of studies and review of company's critical appraisal

The company did not submit a defined section of text detailing their critical appraisal. They do however acknowledge that one of the main limitations of the published evidence is that the studies were not randomised controlled trials, and that direct comparisons were not possible between the Axonics and the standard care alternative (a non-rechargeable system). Appendix B details the EAC's critical appraisal considerations relating to the clinical evidence (effectiveness and safety) using a checklist adapted from the Critical Appraisal Skills Programme (CASP). Many of the design and reporting weaknesses were common to both studies.

All evidence relating to the Axonics system was from single-arm studies. The company submission included evidence from the NHS standard care comparator technology (the Medtronic InterStim non-rechargeable SNM system). Treatment responder rates were presented in a single table for visual comparison, but there is no indication that robust methods were used to conduct indirect analyses. Keifer et al. (2015) describe methods for indirect analysis, and state that "Nonadjusted indirect comparisons, ie naïve comparisons of individual arms of different trials, are not an appropriate method of analysis".

The only comparative data within the scope of this assessment derives from measures recorded before and after implantation of the Axonics device (therefore studies are classified as single-arm, intra-patient, and observational in design). With no randomised recruitment, there is a risk that variation in patient selection and surgical techniques could have influenced treatment outcomes.

Another crucial limitation of existing studies is a lack of long-term outcome data. The Axonics device was only approved for clinical use in 2016, and clinical effectiveness has not been definitively demonstrated beyond 2 years. Battery life is one of the main issues for consideration when evaluating cost effectiveness.

The RELAX-OAB study included 37 individuals with symptoms of urinary urge incontinence (UUI), and all except one (n=50/51) also had symptoms of urinary frequency (UF). Study authors report these results separately as well as combining them as a composite overactive bladder syndrome (OAB) score. Separation of subgroups is helpful, as treatment effectiveness is known to vary by indication (as confirmed by expert advisors). The ARTISAN-SNM study only includes individuals with UUI.

Although individuals appear to have been prospectively recruited, study authors did not report whether this was consecutive. During fact checking, the company informed us that consecutive recruitment had been used, and that all eligible participants were included in these studies. The company did not provide a description of criteria that would be used in clinical practice to select patients for whom the technology would be most appropriate. Furthermore, study eligibility criteria lacked clarity. For example, RELAX-OAB excluded people with "Any significant medical condition that is likely to interfere with study procedures, device operation, or likely to confound evaluation of study endpoints" (Blok et al. 2017). The EAC considered that this definition could be open to interpretation by site investigators, and could contribute to a relatively high risk of selection bias (especially given that both studies were funded by the company). During fact checking, the company informed us that none of the subjects in the study were excluded because of this criteria, which had been intended to exclude patients unable to operate the device.

McCrery et al. (2019) report that 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, who most often have exhausted medication options before being offered SNM. Expert advice in the UK indicates that those who have failed conservative management and pharmacological treatment would not usually continue to take associated medications. This may be more reflective of a US population where the refractory OAB population is defined as having tried and failed at least 2 medications.

Possible consequences of conducting the ARTISAN-SNM study in a population where some patients continued to take concomitant medication have been proposed as:

- an adjuvant effect (improving overall effectiveness). This is mitigated by the inclusion criteria which requires "no changes to current regimen of medications that affect bladder function for at least 4 weeks" prior to baseline data collection.
- patients cease taking medication during SNM treatment (reducing overall effectiveness).

The company informed the EAC that a post-hoc subgroup analysis was conducted between subjects that took concomitant medications at baseline and subjects that did not take concomitant medications at baseline. There was no statistically significant difference in responder rate results between these sub-groups at any follow-up visit.

Neither study was carried out exclusively in a UK setting and findings may not be generalisable to the UK NHS population. Both clinical studies each

included patients from a single UK site, but did not report the number or proportion of UK subjects. It is assumed that the majority of data originate from other nations; McCrery et al. (2019) also noted the inclusion of private practices. Only 2 of 129 participants (2%) in the ARTISAN-SNM study were male; although urinary incontinence is more common in females, expert advisors estimate that the proportion of males undergoing SNM treatment would usually be around 20%.

Patient histories vary with regard to prior treatment. In ARTISAN-SNM, 13% (17/129) had received botulinum toxin therapy; 13% (17/129) had undergone tibial nerve stimulation; and 7% (9/129) had participated in a previous trial of an external SNM device. These categories were not mutually exclusive. The RELAX-OAB study authors report that a total of 51% of participants had previously tried at least one other third line therapy for OAB. One quarter (25%) had received botulinum toxin therapy; 31% had undergone tibial nerve stimulation; and 20% had previous sling procedures (to treat stress urinary incontinence).

The RELAX-OAB online registration information specified changes in the ICIQ-OABqol score as its primary outcome measure in advance of recruitment. But this record also indicates that multiple quality of life tools were administered (including SF-12, EQ-5D, and I-QoL). The results of these before-and-after comparisons do not appear to have been reported in any of the publications (the same is true of the 'healthcare utilisation' measure). There is a risk of reporting bias, although the company has clarified that the ICIQ-OABqol tool was of most direct relevance to the study population.

A sample size calculation for the ARTISAN-SNM study indicated the requirement of a minimum of 116 people; 129 people were recruited and 113 responded to the initial trial period (3 patients were withdrawn from this study within the first 6 months, for reasons detailed in section 6 – adverse events). McCrery et al. (2019) accounted for this discrepancy by reporting the results of intention-to-treat (ITT) analyses.

The company submission recognised that ITT analyses had not been reported in the RELAX-OAB publications. Within the first 3 months, 3 patients had withdrawn from the study, with a further 5 by 1 year and 3 by 2 years, totalling 11/51 (22%). Of the remaining 40 participants, 3 had missing diary data, which equated to full data being available for 73% (37/51) of the whole study population by 2 years. The company submission includes adjusted analyses using a conservative case analysis, which assume that those individuals with missing data (lost to follow-up or whose devices were explanted) would be considered treatment failures. The EAC agrees that this is our preferred

approach, as it mitigates reporting bias and more closely reflects a ‘real world’ scenario.

The authors of papers relating to the RELAX-OAB study do not refer to having conducted a sample size calculation. Fifty-one people underwent the initial implantation procedure, but numbers within subgroups become progressively smaller; after 1 year the denominator for UUI test responders is n = 26 (n=25 at 2 years). The EAC recommends caution when interpreting claims of significance in these small populations as they may lack statistical power (despite apparent clinical significance in some of the results).

4.3 Results from the evidence base

Results from the literature are summarised in table 3 according to study name; key outcomes are summarised in separate columns. Unpublished data are presented separately in the table to clearly differentiate them from those which have been peer-reviewed.

Table 3. Summary of key results.

Study & associated publications	**Therapy responder rate* (ITT)**	**ICIQ-OABqol score (mean increase)**	**Symptom reduction** (mean numbers ± standard error (SE))	**Satisfaction**	**Adverse events**
ARTISAN-SNM study McCrery (2019), 6 month results.	**Of the initial UUI test responders (n=113), those who responded to therapy at:** **3 months:** 95% (n=107) **6 months:** 95% (n=107; 95% CI 83, 95, p<0.0001) Statistical significance findings refer to change from baseline.	**Composite measure:** 34.2 points **Subscales:** • Concern: 38.6 • Coping: 38.6 • Sleep: 31.4 • Social interaction: 22.6	UUI episodes per day reduced from 5.6 (± 0.3) at baseline to 1.3 (± 0.2) at 6 months. **All participants** 79% reduction in number of UUI episodes per day for all participants. **Therapy responders** Of the therapy responders: • 80% had a minimum of 75% reduction in number of UUI episodes per day at 6 months • 34% were dry.	93% of people reported being "satisfied" with treatment 92% would undergo r-SNM therapy again	10 device-related AEs (n = 10) at 6 months. 6 episodes (n = 6) of discomfort due to stimulation (resolved with reprogramming). 2 episodes (n = 2) of pain at the neurostimulator site (resolved spontaneously). 1 lead migration (successfully revised). 3 people were withdrawn from the study within 6-months: 2 devices were explanted (1 postoperative wound infection; 1 because of pain unrelated to device). 1 person died (not device related).
Unpublished data					
ARTISAN-SNM study Lane et al, 12 month results, unpublished conference abstract and poster.	**Of the initial UUI test responders (n=113), those who responded to therapy at:** **12 months:** 94% (n=106; 95% CI 83, 94, p<0.0001)	34 points (p < 0.0001).	UUI episodes per day reduced from 5.6 (± 0.3) at baseline to 1.4 (± 0.2) at 12 months (p < 0.0001). 77% responders had a minimum of 75% reduction in the number of UUI episodes per day; 29% were dry.	93% reported treatment satisfaction.	No serious device related incidents were reported. The total number of explantations at 12 months is reported by the company as 3% (of 129), but after excluding test non-responders this proportion is reduced to <1%. There was also 1 suspected lead fracture which required revision.

Study & associated publications	Therapy responder rate* (ITT)	ICIQ-OABqol score (mean increase)	Symptom reduction (mean numbers ± standard error (SE))	Satisfaction	Adverse events
RELAX-OAB study Blok (2018a), 3 month results Blok (2018b), programming settings at 3 months. Blok (2019a), 12 month results	**Of the initial OAB test responders (n=34), those who responded to therapy at:** **3 months:** 91% (n = 31) **12 months:** 88% (n = 30)	**3 months:** 27.3 points, (p < 0.0001). **12 months:** 21.1 points (p < 0.0001). Subscale scores also showed significant improvements (p < 0.0001).	**6 months:** In test responders, voids reduced by 6.6 per day. Incontinence episodes decreased by 6.3 ± 4.4 leaks per day. **12 months:** In UUI test responders, leaks reduced from 8.3 (± 0.8) per day at baseline to 1.8 (± 0.5) per day (p < 0.001). In test responders with UF, voids reduced from 14.3 (± 1.1) per day at baseline to 8.0 (± 0.5) per day (p < 0.0001). Devices were explanted from 2 people between 6 and 12 months due to lack of efficacy.	**3 months:** 77% of all participants reported being very or moderately satisfied with their therapy. **12 months:** 77% of all participants reported being moderately satisfied with their therapy.	No serious adverse device events were reported. 20 device-related AEs occurred in 13/51 people. 7/20 AEs occurred in the first 2 weeks. Undesirable or uncomfortable stimulation (13 events, n = 10), all resolved with reprogramming. Pain at the IPG implant site (n = 1) was resolved with reprogramming. Lead migration (n = 1) occurred between 3 and 6 months post-implant. Procedure-related serious adverse event: Infection at the IPG site (n = 1); device explanted after 3 weeks.

Study & associated publications	Therapy responder rate* (ITT)	ICIQ-OABqol score (mean increase)	Symptom reduction (mean numbers ± standard error (SE))	Satisfaction	Adverse events
Unpublished data					
RELAX-OAB study Blok (2019c), unpublished manuscript; 2 year results Blok (2019b), 2 year results (published conference abstract & poster) were identified by the EAC after the original literature searches.	**Of the initial test responders (n=34), those who responded to therapy at:** **2 years:** 79% (n=27)	Mean increase of 29 points ($p < 0.0001$). Subscale scores for concern, coping, sleep and social interaction also showed significant improvements ($p < 0.0001$).	**2 years:** In UUI test responders, leaks per day reduced from 8.3 (± 0.8) at baseline to 1.7 (± 0.5) at 2 years (80% reduction, $p < 0.0001$). In UF test responders, voids per day reduced from 14.3 (± 1.1) at baseline to 7.3 (± 0.4) at 2 years ($p < 0.0001$). Devices were explanted in 4/51 people (8%) due to lack of efficacy, but this included only 1 initial test responder (1/34; 3%).	At 2 years, 93% (n = 25/27) of therapy responders were satisfied with their therapy.	21 device related AEs in 13 people (26%) over 2 years. 8 occurred within 2 weeks of implantation. Undesirable or uncomfortable stimulation: 13 events in 10 people (20%), resolved with reprogramming. Pain at neurostimulator implant site: n = 1 Lead migration: n = 1 Lead fracture: n = 1 Explantation at 2 years: n = 7/51 (14%): • Infection at incision site: 1 • Lack of efficacy: 4 • High impedances: 1 • MRI scan: 1 (device had not yet been approved for MR scan)

*For definition of therapy responder rate, refer to table 2.

Therapeutic responder rate

McCrery et al. (2019) report data collected 6 months after permanent implantation of the Axonics SNM system in people with urinary urgency incontinence who participated in the ARTISAN-SNM study. The primary outcome measure for this study was the therapeutic responder rate (proportion of participants reporting ≥50% reduction in UUI episodes per day) according to 3-day urinary diary entries at 6 months as compared with baseline records. Based on analysis of the whole UUI population, 116 of 129 people (89.9%) were reported to be therapy responders at 6 months. The company submission indicated that a 1-sided binomial test for responder rate >50% resulted in a p-value less than 0.0001 (95% confidence intervals (CI) for responder rate 83.4%, 94.5%). However, this primary outcome measure included individuals who had not responded to treatment during the initial trial period 1 month after implantation. If the test non-responders are excluded (to better reflect the population of interest), the responder rate increases to 95% at 6 months ($p<0.0001$; 95% CI 88.8%, 98.0%), and remains at 94% after 1 year ($p<0.0001$; 95% CI 87.7%, 97.5%).

Although not considered to be the primary outcome, responder rates for the RELAX-OAB study were reported according to indication (UUI, UF, and as a composite measure of overall change in symptoms of OAB). Focusing again on ITT results for those who had responded during the initial trial period, therapy responses for the whole OAB population were 91% (n=31), 88% (n=30), and 79% (n=27); at 3 months, 1 year, and 2 years respectively. Corresponding proportions for symptoms of UUI were 75% (n=21), 89% (n=25), and 79% (n=22), and for UF symptoms were lower at 73% (n=24), 67% (n=22), and 64% (n=21).

The EAC has produced figure 1 to illustrate these therapeutic responder rates for test responders from both studies, based on ITT analyses. A flow diagram is available for reference with details of response rate calculations for the RELAX-OAB study sub-groups (Appendix C). Note that 1-year (12 month) ARTISAN-SNM and 2 year (24 month) RELAX-OAB results originate from unpublished data.

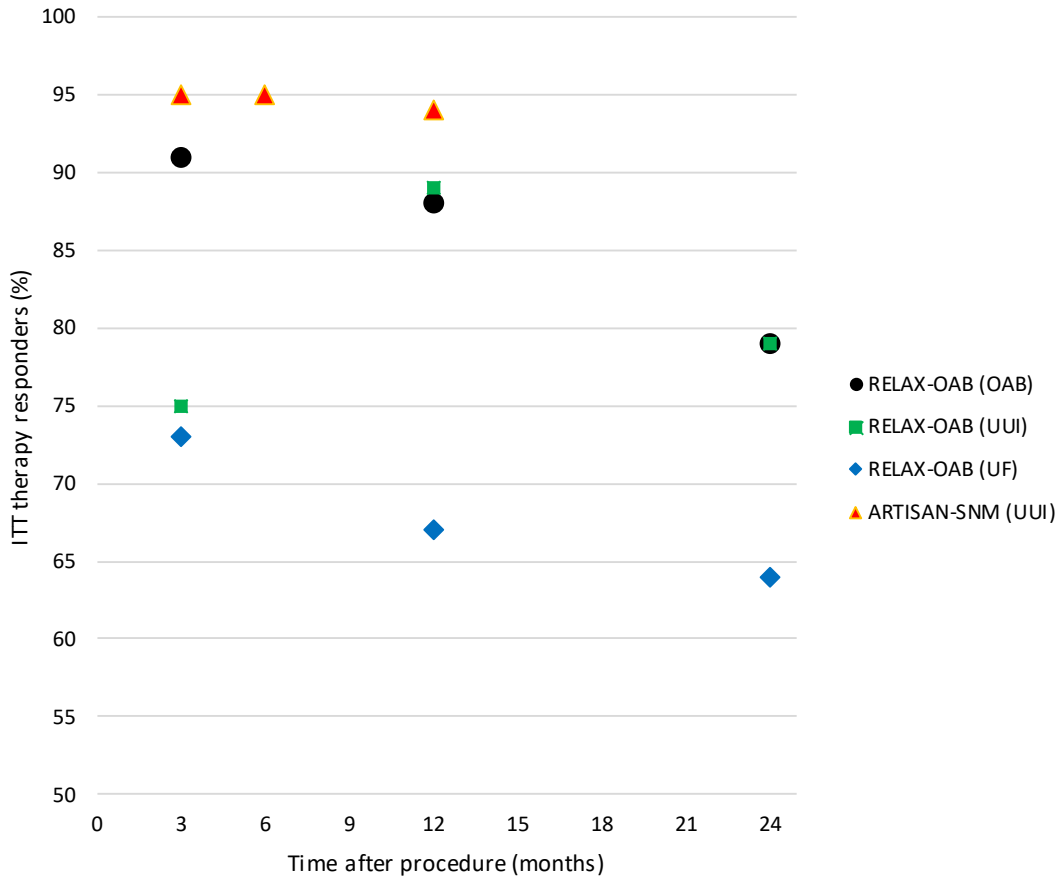

Figure 1. ITT therapy response rates over time. These results include only those who reported a reduction in symptoms of >50% during the initial trial period.

Change in symptoms of overactive bladder

The ARTISAN-SNM study reports mean (± SE) baseline daily UUI episodes (leaks) as 5.6 ± 0.3, reducing to 1.3 ± 0.3 after 6 months, and 1.4 ± 0.2 at 1 year. A 2-sided Wilcoxon signed rank test indicates that changes from baseline were significant ($p<0.0001$). Average (± SE) daily UUI episodes in the RELAX-OAB UUI test responders were 8.3 ± 0.8 at baseline, and 1.8 ± 0.5 after 1 year; the magnitude of reduction was reported as 6.3 ± 4.4 at 6 months, and 5.3 ± 0.9 at 1 year ($p<0.0001$).

Urinary frequency (average voids per day) in the ARTISAN-SNM UF patients reduced from 11.6 ± 0.3 at baseline to 8.7 ± 0.2 at 6 months ($p<0.0001$). In the RELAX-OAB UF patients, the mean (± SE) voids per day were 14.3 ± 1.1 at baseline, reducing to 8.0 ± 0.5 by 1 year ($p<0.0001$).

Quality of life

The primary outcome measure for the RELAX-OAB study was the change in quality of life (ICIQ-OABqol) score at 3 months. The scores for this measure range from 0 to 100; an increase of 10 points is considered to represent a minimum clinically important difference (MCID) (Coyne et al. 2006). ICIQ-OABqol is reported as a composite measure, with subscales of Concern, Coping, Sleep and Social Interaction (each also having a score range of 0-100).

Absolute before-and-after quality of life measures have not been provided by the authors in most of the associated publications – results are reported as the 'average' magnitude of change (increase in ICIQ-OABqol scores); presented graphically (with standard error bars); or simply described as a 'significant improvement' (referring to both clinical and statistical significance). A summary of published quality of life findings is presented in table 4.

Table 4. Change in quality of life from baseline. A plus (+) symbol indicates average increase in score from baseline. NR = not reported. 2-year (24 month) RELAX-OAB results and 1-year ARTISAN-SNM data are derived from unpublished materials.

Study (population)	**ICIQ-OABqol Measure**	**Months after procedure (average change in score)**			
		3	**6**	**12**	**24**
RELAX-OAB (OAB including UUI & UF - test responders only)	**Composite**	**+27.3**	**+26.2**	**+21.1**	**+29**
	Concern	"Significant improvement"	"Significant improvement"	"Significant improvement"	+31
	Coping	"Significant improvement"	"Significant improvement"	"Significant improvement"	+34
	Sleep	"Significant improvement"	"Significant improvement"	"Significant improvement"	+26
	Social interaction	"Significant improvement"	"Significant improvement"	"Significant improvement"	+22
ARTISAN-SNM (UUI - all implanted patients)	**Composite**	**"Significant improvement"**	**+34.2* (29.9, 38.5)**	**+34* (29.9, 38.8)**	NR
	Concern	"Significant improvement"	+38.6	+39	NR
	Coping	"Significant improvement"	+38.6	+39	NR

	Sleep	"Significant improvement"	+31.4	+33	NR
	Social interaction	"Significant improvement"	+22.6	+22	NR

*Asterisk indicates statistically significant result based on two-sided Wilcoxon signed rank test for paired observations for change from baseline ($p<0.0001$). 95% confidence intervals are specified in brackets where reported by the company or study authors.

Subjective patient satisfaction scores are summarised in table 3. Carer satisfaction was not reported in any of the published evidence.

5 Adverse events

Numbers of adverse events (AEs) reported by the studies have been included in table 3. No serious device- or procedure-related AEs were reported, and there were no unanticipated AEs in either study. Device-related AEs occurred on 10 occasions in 10 of 129 people (8%) after 6 months (ARTISAN-SNM study), and as 21 events in 13 of 51 people (26%) after 2 years (RELAX-OAB study). The most commonly-reported AEs were discomfort associated with stimulation (6 AEs in 6 people (5%) at 1 year in ARTISAN-SNM study; 13 events in 10 people (20%) at 2 years in RELAX-OAB study); all of which were resolved with reprogramming.

Including test non-responders, devices were explanted from 4 of 129 people (3%) after 1 year (ARTISAN-SNM) and from 7 of 51 people after 2 years (14%). Of these 11 procedures, 2 were a result of early wound infection at insertion sites (1%), 1 because of pain (unrelated to the device), 1 due to need for MRI (prior to regulatory approval for MRI compatibility), 1 because of high impedances (suspected lead fracture), and 6 due to lack of efficacy (at least 3 of whom had been test non-responders).

There was 1 lead migration reported within the first 6 months of each study, both resolved as a result of lead revision procedures. In the company submission and the ARTISAN-SNM study (n=129), "Unintended nerve activation" was reported at 2% after 1 year; no further details were provided. Discomfort/heating during charging was reported in 1% of the same population. One patient died within the first 6 months, but this AE was not considered to be device-related.

Pain at the implant site occurred in 2% in both studies within the first 6 months (2 episodes, n=2 ARTISAN-SNM; n=1 RELAX-OAB); 1 resolved with reprogramming and 2 resolved spontaneously. Expert advisers have speculated that long-term implantation may be associated with an increased risk of pain as a result of lead migration or IPG movement, or that there may be issues with long-term implantation of a lithium device. Conversely there is

anecdotal evidence that the smaller size of the Axonics IPG is associated with a reduced risk of pain and discomfort when compared with larger non-rechargeable devices. Experts with experience using other SNM systems believe that tolerability is likely to be sustained in the longer term.

The company's submission observes that adverse events are not expected to differ substantially between devices; this was also confirmed by Expert Advisers to NICE. A possible exception is that the long-term incidence of surgical complications could be reduced with rechargeable systems, as battery replacement procedures are anticipated to be required less frequently.

6 Interpretation of clinical evidence

Despite limitations of the available evidence (as described in section 5.2), the "before and after" improvements seen in the Axonics studies were consistent with the views of expert advisors. There appears to be little doubt that SNM can offer significant improvement in control of OAB symptoms and quality of life when compared with a "do nothing" scenario, at least within the first two years. The symptoms of urinary urge incontinence were more likely to show improvement than those associated with urinary frequency, although of course treatment 'success' is dependent on how improvement is defined.

The subjective patient satisfaction scores suggest promise, but the tools and methods may not have been validated and their quality has not been ascertained. More reliable are the quality of life results which were based upon the ICIQ-OABqol validated questionnaires.

There is uncertainty about how selection criteria were applied at study sites. Eligibility limitations may mean that the samples do not accurately represent the target population, and outcomes may not be directly generalisable to the UK NHS. Some expert advisers consider that surgical technique and associated equipment (such as use of curved stylets) may have an impact on effectiveness of treatment.

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. As well as longer

battery life, there are other potential benefits associated with the Axonics system, such as its compatibility with full-body MRI scanning. These will be considered in the review of economic evidence by modelling the long-term cost-effectiveness of the rechargeable technology.

6.1 Integration into NHS

The place of the Axonics system in the patient pathway is straightforward, as it would simply be an alternative to the current non-rechargeable system. The implantation procedure is near-identical. In general, expert advisers do not anticipate there being differences in the requirement for outpatient follow-up appointments or long-term monitoring.

Surgical and patient training are also similar to current practice. The company provides in-person presence during every implantation procedure, and ongoing support. Users occasionally require re-training in order to charge the battery correctly, but most are able to manage recharging and use of the system.

The patient remote control is a portable device which can be attached to a key-ring. Neither the company nor clinical experts were aware of reports of accidental activation or de-activation of the system, although one expert adviser suggested that it is a risk which should be mitigated through patient education. Changes in amplitude are gradual and the highest level remains tolerable to users, so there is a low risk of discomfort if the remote control were unintentionally triggered. Switching the system off would be expected to lead to a recurrence of OAB symptoms.

The company proposes that the environmental impact of the rechargeable device would be reduced as a consequence of less frequent replacement of IPG devices. The EAC is not aware of any further detail or evidence supporting this assumption.

6.2 Ongoing studies

No additional ongoing studies were identified by the EAC. ARTISAN-SNM is due to complete in June 2020 and RELAX-OAB in February 2022.

7 Economic evidence

7.1 Published economic evidence

7.1.1 Search strategy and selection

The company undertook a separate comprehensive search for economic evidence in the following databases: Embase, Medline/Pre-Medline, Health Technology Assessment Database, and NHS Economic Evaluation Database, with searches tailored to each databases. The EAC noted a typographical error in line 22 for Health Technology Assessment database search and NHS Economic Evaluation search: 'scaral' instead of 'sacral', although the EAC corrected this no additional relevant literature was identified. The EAC conducted a single search for both clinical and economic evidence, details of this and of the company's search are provided in Appendix A. 'The company designed their searches to capture all economic studies of sacral nerve stimulation for overactive bladder. This yielded 19 studies which were summarised in the economic submission and provided information about performance of the comparator device. None of these studies met the requirements of scope, however two contained relevant information for the economic model and are briefly reported on by the EAC. The EAC did not identify any economic evidence directly concerning Axonics.

7.1.2 Published economic evidence review

The economic evidence included by the company is not directly relevant to the scope and has been excluded by the EAC. Only one paper (Freemantle *et al.* 2016) included by the company was set in the UK, but is a cost-effectiveness for onabotulinumtoxinA versus supportive care in the treatment of overactive bladder. There are some costs for SNM that are included in the supportive care arm. There was also only one economic model reported (Noblett *et al.* 2017) that compared rechargeable with non-rechargeable neuromodulation devices. Although it did not consider the Axonics Neuromodulation System, and was not set in the UK, it was used by the company as a base for the submitted model, and is therefore described briefly.

Freemantle *et al.* (2016) list a number of costs and assumptions for provision of SNM. They assume a discontinuation rate of 7.1%; that 23% of patients with the device would undergo successful surgical revision; that individuals would have 3 clinical visits for programming per year and batteries would be replaced every 7 years.

Noblett *et al.* (2017) is a cost-consequence model with quarterly progression between three health states (on SNM therapy, discontinuation of therapy and

death). The model evaluates the patient population with characteristics similar to those from the InSite study. Noblett *et al.* (2017) compares a non-rechargeable with a rechargeable device. Assumptions about longevity of the neurostimulator device was based on the reported lifetime of the InterStim device for the non-rechargeable device and spinal cord stimulation systems (Eon Mini Rechargeable IPG, Nevro Senza SCS system) for the rechargeable device. The EAC performed a quality assessment of Noblett *et al.* (2017) study (Appendix D) and concluded that it has potentially serious limitations: data sources are not well reported and the data stated in the model is hard to identify within referenced papers. This has partly been addressed by an updated reference list provided by the company. Not all relevant costs are detailed, for example types and amounts of antibiotics used for infection. The study was in part supported by Axonics Modulation Technologies, Inc. Noblett *et al.* (2017) found that in a US setting the rechargeable neurostimulator may lead to cost savings in managing overactive bladder over the course of treatment, due mainly to reduced need for replacement devices.

7.1.3 Results from the economic evidence

The economic evidence included by the company is not relevant to the scope and has been excluded by the EAC; the EAC did not identify any relevant literature.

7.2 Company de novo cost analysis

7.2.1 Economic model structure

The model evaluates people who are candidates for SNM – patients with overactive bladder syndrome who have not responded to drug treatment or conservative management or are unwilling to accept the risks associated with botulinum injection.

The model is based on a previously published model by Noblett *et al.* (2017) adapted for UK setting. Appendix D presents the differences between Noblett *et al.* (2017) and the model submitted by the company. The model is adapted to use UK costs, and for the Axonics rechargeable device lifetime of 15 years rather than 10 years for an alternative rechargeable device. The adapted model only applies lead migration events at the initial event, rather than at each implantation. It is also removes the assumption that 20% of patients with a rechargeable device will change to non-rechargeable after 4-4.5 years. Reporting by Noblett et al (2017) concentrates on a business impact model, and a phased uptake of rechargeable devices.

The model structure is from an NHS and personal social services perspective. The time horizon of 15 years matches the intended battery life of

rechargeable device and the EAC agree that it will capture all relevant costs associated with this device. A longer time horizon is included in sensitivity analysis however there may be more significant technology changes over this length of time. The discount rate of 3.5% is applied as per NICE Guideline for the methods of technology appraisal.

The structure is a Markov model with a 3 month cycle, comparing two SNM devices – rechargeable Axonics (Axonics Modulation Technologies, Inc.) and a non-rechargeable device (InterStim, Medtronic, Inc.). The model starts from device implantation (pre-testing for the patients' response is explored in the sensitivity analysis). Three health states are considered – on SNM therapy (either rechargeable or non-rechargeable); off SNM therapy (discontinuation) and dead. The model does not use typical Markov trace where calculations are presented for each health state. Instead each parameter is described separately and all costs summed up. Patients can move between states based on transition probabilities: mortality and per-cycle therapy discontinuation. The calculation for discontinuation rate is applied every cycle to those still using SNM therapy. Once the proportion in the SNM and discontinued state is calculated for each cycle, the mortality rate is applied, to give a final numbers in each state, including the number of patients who have died.

The cost calculations are presented for 15 years. Additional modelling was provided for scenarios including a 30 year time horizon, testing prior to implant and a business impact model. The details of these are included separately in Appendix G, but results were not included in the company submission. The model matches the scope of the assessment report and the clinical pathway, with the addition of the combined arm.

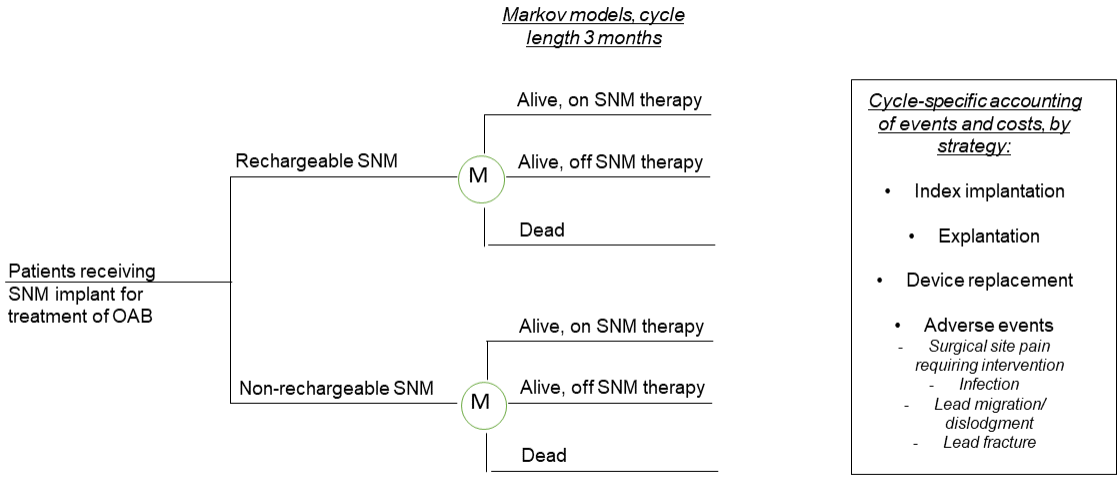

Figure 2: Model schematic taken from Appendix B in the company economic submission.

The model has some additional functionality not included in the submission:

- Business impact analysis
- Modelling for a gradual uptake of rechargeable technology.
- A decision tree exploring the testing options to evaluate response to SNM, along with associated outcomes and costs.

These results are not included in the submission or the body of the EAC assessment report, except for a brief mention of testing, which is included as a scenario. A discussion of pre-implantation testing, including EAC base case results are included in Appendix G.

Table 5: List of assumptions included in the economic model.

Assumption	EAC comment
Assumptions identified in the company's economic submission	
No difference in SNM therapy effectiveness and discontinuation between rechargeable and non-rechargeable device.	There are no comparative studies between the two devices, however they are both intended to work in a similar way. The EAC has modelled two scenarios: 1 using clinical inputs from the submitted clinical evidence for both arms. 2. Using clinical evidence for each arm from studies based on the appropriate device.
Differences in the rechargeable and non-rechargeable device lifetimes lead to a reduced need for rechargeable device replacements and a reduction in procedure related adverse events.	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. Axonics claim a 15 year battery life based on bench testing and CE marking. The EAC carried out Threshold testing of the model, and Axonics is cost saving in the submitted base case at a lifetime of approximately 6 years

There are no differences in testing procedures and test outcomes prior to full implantation of SNM device. The testing procedure is not modelled	A scenario analysis explores extra costs and resource use associated with pre-implantation testing for effectiveness of SNM therapy in this group of patients. The EAC agrees with the assumption as the patient pathway, costs or resource use associated with testing are the same for both devices.
Additional assumptions identified by EAC	
No difference in the rate of adverse events between the rechargeable and non-rechargeable device.	There is no comparative data available on the two devices. The EAC use data from both InterStim and Axonics studies in their base case, and the impact is further investigated in EAC scenario analysis
Adverse events happen in the same cycle as the procedure, and do not occur subsequently.	This is probably justified for infection, as these will be procedure related. Lead migration, breakage, and pain may not be related to procedure and may continue throughout the model life. Additional scenario modelling by EAC.
Likelihood of infection, or pain is reduced at subsequent procedures.	This is a conservative assumption, as reduced adverse events reduce the costs associated with replacements. This reduces the impact of a longer device lifetime.
Procedures are carried out as inpatient admissions (1 day) rather than day cases.	Day cases have a lower cost, and this assumption favours the intervention, but only slightly. This is changed in the EAC base case, following consultation with clinical experts
Efficacy is 100% for patients that continue in therapy. Costs for incontinence are only accrued by patients who have discontinued	The discontinuation rates are the same for both devices, therefore this will have no impact on the cost difference.

7.2.2 Economic model parameters

The 3-months transition probability for mortality is derived from UK lifetables for 2015-2017 with gender-specific calculations. The 3-month probability of therapy discontinuation during the first year is based on study by Noblett *et al.* (2016). For subsequent years, the probability was calculated from information

in both Noblett *et al.* (2016) at 1-year and Chughtai *et al.* (2015) at 5 years and assumed for second and following years.

The clinical paper by Noblett et al. (2016) reports the results from the first 12 months of the InSite trial. The patients were recruited and randomised to receive either the InterStim device or standard medical therapy. After an initial 6 months, patients receiving standard therapy were implanted with the InterStim device and followed with all other patients. The study included 340 patients with the diagnosis of overactive bladder who were tested, 272 of these patients received implants. The trial evaluated therapeutic success (improvement in average leaks or voids per day or return to normal voiding frequency). Other outcomes included Health-Related Quality of Life, assessment of sexual function at 12 months and adverse events.

Clinical parameters and variables

Most of the clinical parameters and their distribution are derived from the InSite study (Noblett *et al.* (2016)) which were also used for the economic evaluation of rechargeable and non-rechargeable devices in the US setting (Noblett *et al.* 2017). However, values for gender distribution, InterStim technology lifetime, and frequency of programming visits are derived from other sources (Suskind *et al.* (2013), Cameron *et al.* (2013), Freemantle *et al.* (2016). These studies are briefly summarised in table 6.

Table 6. Clinical parameters used in the company's model and any changes made by the EAC.

Variable	Company value	Source	EAC value	EAC comment
Patient age, yrs.	57	Noblett et al, 2016	Unchanged	Varied in sensitivity analysis
Discontinuation rates, for any reason (3 month cycle)				
Therapy discontinuation, first year, Axonics	1.22% (based on 4.7% (13/272) in 1st year)	Noblett et al, 2016	1.55%	Blok (2019c)
Therapy discontinuation, first year, comparator	1.22% (based on 4.7% (13/272) in 1st year)	Noblett et al, 2016	1.22%	Comparator.
Therapy discontinuation, subsequent years, both arms	0.08% (based on 6.0% at 5 yrs, and 4.7% at 1 yr)	Chughtai et al, 2015	0.83%	Chughtai 2015, corrected at 17.3% at 5 years
Adverse events – Infection at implant site (cycles with implant procedure only)				
Implant site infection, 1st procedure, Axonics	4.48%	Brueseke et al, 2015	1%	McCrery (2019)
Implant site infection, 1st procedure, Comparator	4.48%	Brueseke et al, 2015	Unchanged	
Implant site infection, 2nd + procedures, both arms	50% of 1st procedure	Assumption (Noblett et al, 2017)	Unchanged	Same assumption
Device replacement, both arms	37% of infections	Brueseke et al, 2015	Unchanged	
i.v. antibiotic treatment needed, both arms	30% of infections	Brueseke et al, 2015	Unchanged	
No events explicitly modelled for patients not requiring replacement or antibiotics				
Adverse events – Pain at implant site (cycles with implant procedure only)				

Surgical site pain requiring surgical intervention, 1st procedure, Axonics	4.04% (11 of 272 subjects in InSite)	Noblett et al, 2016 - InSite - PI reported data	2%	McCrery (2019)
Surgical site pain requiring surgical intervention, 1st procedure, Comparator	4.04% (11 of 272 subjects in InSite)	Noblett et al, 2016 - InSite - PI reported data	Unchanged	
Surgical site pain, 2nd + procedures	25% of index procedure input	Assumption, clinical experts	Unchanged	
Revision	82%	Noblett et al, 2016 - InSite - PI reported data	Unchanged	
Explantation	18%	Noblett et al, 2016 - InSite - PI reported data	Unchanged	
Adverse events – Lead migration, dislodgement or breakage. 1st cycle only				
Lead migration/ dislodgment, Axonics	1.10% (3 of 272) subjects in InSite)	Noblett et al, 2016 - InSite - PI reported data	1%	Lane (2020)
Lead migration/ dislodgment, comparator	1.10% (3 of 272)	Noblett et al, 2016 - InSite - PI reported data	Unchanged	
Need to replace lead in case of dislodgment/ migration, both arms	100%	Noblett et al, 2016 - InSite - PI reported data	Unchanged	
Lead fracture, both arms	1.47% (4 of 272)	Noblett et al, 2016 - InSite - PI reported data	Unchanged	No data for Axonics
Planned replacement of device battery				
Required stimulator replacement, Axonics	15.0 yrs	Company claim based on testing	Unchanged	

Required stimulator replacement, comparator	4.4 yrs	Cameron et al., 2013	Unchanged	
Replacement interval for remote control and charging system (years)				
Patient remote, Axonics	7.5 yrs		Unchanged	
Patient remote, Comparator	15.0 yrs		Unchanged	
Charging System, Axonics	7.5 yrs		Unchanged	
Discontinuation rates (for any reason, including adverse events), 3 month cycle				
Programming visits, first year, both arms	2.14	Cameron et al, 2013	Unchanged	
Programming visits, subsequent years, both arms	0.74	Cameron et al, 2013 (based on yr. 2 data)	Unchanged	

Discontinuation rates

Discontinuation rates are calculated 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. They are assumed by the company to be the same in both arms of the model.

Chughtai et al (2015) report results for a retrospective study of 1,474 Medicare patients who underwent SNM procedures in the USA between 2001 and 2011. The study reported 90 day and 5 year complications and discontinuation rates. All devices were non-rechargeable.

The company have used a 1 year discontinuation rate of 4.8% from Noblett 2016. The discontinuation rate for years 1-5, which was also applied to all subsequent years, was calculated based on information provided in Chughtai 2015. The publication reports the rate of device removal of 17.3% and device replacement of 11.3%. The company assumed that device replacement is subsequent to device removal and calculated the rate of discontinuation equal to 6% for year 5 (17.3% minus 11.3%). The difference between year 5 (6%) and 1 year (4.8%) was used to calculate the rate for year 1-5.

The EAC disagree with this interpretation of Chughtai 2015. The text and graph (fig 3 in paper) shows that the replacement and removal rates are reported as separate events and result in a composite figure of 26.1% at 5

years who have had at least one replacement or removal procedure. In this case, the removal rate of 17.3% at 5 years is equal to a discontinuation rate and this value should be used in the model. The EAC have corrected this in the EAC base case model, to give a value of 12.5% over 4 years (17.3% minus 4.8%) and applied this rate from year 1 onwards.

The cumulative discontinuation of therapy in the submitted model is calculated as the sum of all probabilities from previous transition periods and does not take into account the actual numbers of patients on therapy. The EAC have corrected this calculation to apply the correct discontinuation probability for each cycle to the number of patient currently in therapy. The overall impact is small.

An alternative to assuming the same rates in both arms, would be to use the reported adverse events and discontinuation rates from the clinical evidence on Axonics, as summarised in table 7 for the Axonics arm of the model. The EAC have used this approach for the base case, but have presented the use of different clinical data in scenario analyses.

Discontinuation rates for Axonics are taken from the two year results for the RELAX-OAB study (Blok et al. unpublished). This reports 7 explants at two years, however we have excluded 3 of these that were due to lack of efficacy in non-test responders. In normal practice these patient would not have received a full implant. The EAC has used 4/34 responders (11.8%) as a conservative rate calculation. Two explants were clearly reported as being in test responders, the remaining two were due to implant site infection and an early loss of efficacy after an initial response. As no longer term data is available for Axonics, the same rate is used for both arms after year 2.

Table 7. Clinical parameters from studies in the submitted clinical evidence, reported for the follow-up period as stated.

Study	Device	Follow-up	N implanted (responder only for Axonics)	Discontinue	Pain	Implant site infection	Lead migration
ARTISAN	Axonics	6 months	116		<2%	<1%	<1%
RELAX	Axonics	2 years	34	11.8%			
Noblett 2016	InterStim	1 year	272	**4.8%**	**4.04%**	3%	**<1%**
Brueseke 2015	InterStim	1 year	669 (implants)			**4.48 %**	
Chughtai 2015	InterStim	90 days	1,474	1.2%		0.7%	

Chughtai 2015	InterStim	5 years	1,474	17.3%			

Adverse events

Four types of adverse events were included in the analysis: infection, pain, lead migration and lead fracture. All adverse events assumed to have the same rates for both arms of the model. The probabilities of three of adverse events (surgical site pain, lead migration/dislodgment and lead fracture) were derived from the InSite study (Noblett *et al.* 2016) and additional data provided to the company by the principal investigator, Dr Karen Noblett.

There is an assumption that infection and pain will be less likely at replacement procedures than the initial implant, however there is no explanation of this other than clinical opinion. For surgical site infection and surgical site pain, the rates are applied at the initial implant (index) procedure and at a reduced rate during each subsequent replacement procedure taking into account the actual numbers of replacements performed, without patients who moved to 'dead' health state. It is assumed that no surgical site pain or infection occurs in cycles that do not have a surgical procedure.

Surgical site infection: The probability of surgical site infection was obtained from retrospective analysis of mixed cohort of patients which included those with faecal incontinence (Brueseke *et al.* (2015); a population not included in the scope).

Surgical site infections were modelled as being either treated by intravenous antibiotics with an inpatient stay of 4 weeks (30% of infections) or with the replacement of entire device (37% of infections). Brueseke *et al.* (2015) also reported treatment by oral antibiotics, however this was not included in the model.

The probability of having a replacement device due to infection was based on the number of patients reported by Brueseke et al. (2015) with infections that required explantation of the device. Brueseke *et al.* (2015) do not report if these patient received a replacement device either at the time of explanation or subsequently.

These parameters re-occur in the model only in cycles where a replacement device is implanted.

The EAC used information from the ARTISAN study, reported at 1 year for infection, pain and lead migration. The ARTISAN study reported a less than 1% rate of infection at 1 year.

Surgical pain: Treatment includes revision surgery and explanation surgery, with the majority (82%) being resolved by revision. This data is taken from Noblett et al. 2016, with the number of revisions and explantation having been reported to the company by the study principal investigator. These parameters re-occur in the model only in cycles where a replacement device is implanted.

The EAC used information reported by McCrery et al (2019) for the ARTISAN study of less than 2% rate of pain at the surgical site at 6 months.

Lead migration, dislodgement or fracture: These rates are only applied at initial implant (index) procedure. The EAC does not agree that this is appropriate. The model published by Noblett at al. (2017) states that patients could experience adverse events associated with subsequent procedures, including lead dislodgement, migration or fracture. Consultation with clinical experts confirmed that adverse events with leads could occur throughout the lifetime of the device, often associated with injury or impact. The EAC have applied the rate at each cycle of the model in the revised EAC base case.

Parameters for lead migration and lead fracture were reported to the company by the principal investigator of the InSite study, and values appear higher than reasonable from the information reported within the paper. The paper states that Adverse events, such as lead fracture and lead migration/dislodgment, had an occurrence rate of <1% whereas the model input are 1.47% and 1.1%, respectively.

The EAC have used lead migration data from the ARTISAN study (McCrery et al. 2019) of less than 1% rate of lead migration at 6 months, and information from an unpublished conference presentation for unchanged results at 1 year.

7.2.3 Resource identification, measurement and valuation

Resource use is based on the direct cost of implanting and management of rechargeable and non-rechargeable devices as well as associated adverse events. The technology would not change any aspects of the patient pathway or current practice and is assumed to be as effective as current device. The company did not identify any extra resource use associated with the implementation in NHS.

All procedures have an associated cost from the National Schedule of Reference Costs (2017-18) and an additional cost for each device component.

The technology costs (device and accessories; excluding VAT) of both rechargeable and non-rechargeable device were obtained from NHS Supply Chain (September 2019).

For both devices, replacing the battery involves replacing the entire implanted pulse generator. Following an adverse event, there is also the potential for the entire system to be replaced. Whenever a rechargeable system is replaced, a new charger is included in the costs.

The Axonics device has additional resources including a charger and the tined lead extension.

The Tined Lead extension is utilized to connect the Tined Lead to the External Neurostimulator during test phases prior to implant.

Table 8 shows how components were costed in the submitted model. During fact check the company identified differences between the model and their expected use of components. The EAC have not changed the base case, but have added an additional scenario reflecting this information. There is only a small impact on the model outcomes.

Table 8: Resources required during each procedure, as in submitted model.

	Tined Lead (TL) Introducer Kit	Implanted Pulse Generator (IPG)	Tined leads (TL)	Charger	Percutaneous Nerve Evaluation (PNE) KIT	Trial Stimulator	Tined Leads (TL) extension	Patient remote control
Testing	✓		✓		✓	✓	●	✓
Initial implant procedure	✓	✓	✓	●				✓
Replacement due to infection	✓	✓	✓	●				
Replacement due to pain	✓	✓	✓	●				
Replacement due to battery		✓						
Lead revision	✓		✓			✓	●	
Lead replacement	✓		✓			✓	●	
Required replacement of Charger System at 7.5 years				●				
✓ required for both devices; ● required for rechargeable device only								

Discontinuation of therapy

The model assumes that there will be 6 GP visits per year after therapy discontinuation from both Axonics and comparator device. Upon therapy discontinuation, the patient is assumed to use continence pads, as opposed to an alternative therapy (such as self-catheterisation). The cost of continence management is comprised of £8 per week for continence pads and £37 per GP consultation. There are no other costs associated with discontinuation.

GP visits and continence pads are not included in the costs for patients who continue SNM therapy.

Table 9 reports all model inputs for resources, and also the values used in the EAC base case. The changes made by the EAC are described in more detail, including the impact on the model results, in the section below.

Table 9: Component costs of SNM devices, and any changes made by the EAC. All costs are excluding VAT.

	Axonics	EAC Value	InterStim	EAC Value	Source
Trial Stimulator Remote	£500.00	Unchanged	[redacted]	[redacted]	NHS Supply Chain
PNE kit	£300.00	Unchanged	[redacted]	[redacted]	NHS Supply Chain
Trial stimulator	£175.00	Unchanged	[redacted]	[redacted]	NHS Supply Chain
IPG	£7,000.00	Unchanged	[redacted]	[redacted]	NHS Supply Chain
Tined Lead (TL)	£1,600.00	Unchanged	[redacted]	[redacted]	NHS Supply Chain
TL extension	£300.00	Unchanged	£ -	£ -	NHS Supply Chain
TL Introducer kit	£500.00	Unchanged	[redacted]	[redacted]	NHS Supply Chain
Patient remote	£500.00	Unchanged	[redacted]	[redacted]	NHS Supply Chain
Charger	£560.00	Unchanged	£ -	£ -	NHS Supply Chain
The EAC checked NHS Supply Chain in October 2019, and amended two values for the comparator arm (trial stimulator and patient remote) All InterStim values were recalculated by the EAC to correct the VAT adjustment					

Table 10: Resources used in the company's model and any changes made by the EAC.

Parameter	Company value	EAC value	Source / comment
Initial implantation procedure and follow-up			
Implantation procedure	£3,531	£1,947	LB79Z, Insertion of Neurostimulator for Treatment of Urinary Incontinence. Changed from inpatient to day case.
Device cost - InterStim	[redacted]	[redacted]	NHS Supply Chain
Device cost - Axonics	£9,660	Unchanged	NHS Supply Chain
Follow-up	£105	Unchanged	WF01A (Consultant led attendance, Urology, follow-up)
Battery replacement and routine equipment changes			
Battery replacement procedure	£672	£670	AA57A Minimal Intracranial Procedure, 19 years and over (day case)
Device cost - InterStim	[redacted]	[redacted]	NHS Supply Chain
Device cost - Axonics	£7,000	Unchanged	NHS Supply Chain
Patient programmer: InterStim	[redacted]	[redacted]	NHS Supply Chain
Patient programmer: Axonics	£500	Unchanged	NHS Supply Chain
Charger, Axonics	£560	Unchanged	NHS Supply Chain
Initial implantation procedure and follow-up			
Device removal (no replacement)	£2,379	£2,372	AA54C Intermediate Intracranial Procedures, 19 years and over, with CC Score 0-1 (day case)
Re-programming - complex	£112	£111	AA57A, General Surgery, Minimal Intracranial Procedure, 19 years and over (outpatient)
i.v. antibiotic treatment (4 wks.)	£5,232	£5,216	WH07B Infections or Other Complications of Procedures, with Multiple Interventions, with CC Score 0-1
Lead revision	£1,500	£1,495	LB80Z Insertion of Neurostimulator Electrodes for Treatment of Urinary Incontinence (day case)
Device cost - InterStim	[redacted]	[redacted]	NHS Supply Chain
Device cost - Axonics	£2,575	Unchanged	NHS Supply Chain
Healthcare costs for patients who are off-therapy			
Cost of incontinence (continence pads), per week	£8	£8	Per NICE CG 171 economic analysis, 2013
Cost of GP surgery consultation	£37	£38	PSSRU 2018, assumption per NICE CG 171
Frequency of GP visits per year in patients who discontinued therapy	6.0	6.0	Assumption per NICE CG 171 econ analysis

Parameter	Company value	EAC value	Source / comment
Testing costs, not used in submitted model, see Appendix G			
PNE, day case	£1,499	£1,495	HRG LB80Z
Device cost - InterStim	[redacted]	[redacted]	NHS Supply Chain
Device cost - Axonics	£475	Unchanged	NHS Supply Chain

Stage 1 tined lead implantation,	£1,500	£1,495	LB80Z Insertion of Neurostimulator Electrodes for Treatment of Urinary Incontinence (day case)
Stage 2 tined lead implantation,	£1,500	£1,495	
Device cost - InterStim	[redacted]	[redacted]	NHS Supply Chain
Device cost - Axonics	£2,575	Unchanged	NHS Supply Chain
Replacement interval for remote control and charging system (years)			
Patient remote, Non-rechargeable (yrs.)	15.0	Unchanged	
Patient remote, Rechargeable (yrs.)	7.5	Unchanged	
Charging System, Rechargeable (yrs.)	7.5	Unchanged	

Summary of EAC changes

The EAC made a number of corrections to calculations and additional changes to the model as summarised in table 11. Most have been discussed individually in the appropriate sections for clinical and resource parameters.

For the inflation calculation, the company had correctly used Cost Price Index, Health as a reference, but had used the table for Weights rather than the Index table, and had not correctly applied these. The EAC have corrected the values, but as most costs were from recent sources the impact on the model was very slight.

Costs were taken from NHS Supply Chain for the comparator, which includes VAT. The company had multiplied this figure by 0.8 to remove VAT, rather than dividing by 1.2. This has been corrected by the EAC and resulted in an increased cost of the comparator, and therefore an increase in cost saving due to Axonics.

Table 11. Summary of EAC changes and impact on model.

	Description	Impact on Model
	EAC Corrections to Model	
1	CPI calculation corrected using CPI index instead of CPI weights.	Minor decrease in cost saving.
2	Correct calculation of cumulative discontinuation.	Minor increase in cost saving.
3	Corrected the cost of the comparator trial stimulator and PR	Increase in cost saving.
4	Recalculation of comparator costs correcting VAT adjustment	Increase in cost saving.
	Additional EAC work on model	
5	Reference costs for the initial implantation changed from Elective inpatient to Day case.	Minor decrease in cost saving.
6	Probability of lead migration/ dislodgement and lead facture changed to be constant throughout the model.	Decrease in cost savings.
7	Use 17% discontinuation rate at 5 years, rather than 6%.	Decrease in cost saving
	Use of Axonics data for the Axonics intervention. Comparator parameters unchanged.	Increase in cost saving.
	EAC Base case results:	Cost saving = £6,273

7.2.4 Sensitivity analysis

The company carried out one way sensitivity analysis on clinical parameters, but not on resources. The submitted model structure assumes that clinical parameters are the same in each arm of the model. This means that the clinical parameters in the one way sensitivity analysis are varied for both the intervention and comparator at the same time, minimising the potential impact. The EAC added one way sensitivity for the device cost and varied each arm separately for the EAC base case. Although no tornado diagrams were included in the submission the EAC have created them for the parameters with the most impact for the submitted model (figure 3) and the EAC base case (figure 4).

The company also modelled different time horizons, and the inclusion of test procedures prior to implantation. The EAC added additional scenarios, including the use of InterStim and Axonics studies for the clinical parameters (where available). The EAC also investigated the assumption that replacement procedures would have fewer adverse events for infection or pain at the surgical site.

The EAC also performed stress tests on the submitted economic model and the results are reported in Appendix E. These investigate the structure of the model, using often unrealistic parameter values.

7.3 Results from the economic modelling

7.3.1 Base case results

Both the submitted model and the EAC base case are cost saving. Although the EAC made a number of changes to the model, none had a large impact on the final cost difference, and in all cases the model remained with Axonics cost saving at 15 years, compared to the comparator non-rechargeable device. Table 12 summarises the results using the same categories as the company submission. The components of each category are noted in Appendix F, however "Device Cost" includes initial implant and scheduled replacement device costs. "Administration Costs" includes the costs of all procedures, follow-up visits, GP visits and re-programming.

Table 12: Summary of base case results.

	Company's results			**EAC results**		
	Technology	Comparator	Cost saving per patient	Technology	Comparator	Cost saving per patient
Without testing						
Device cost (without AE-related device costs)	£14,707	£19,679	£4,972	£13,289	£18400	£5,111
Training costs	0	0	0	0	0	0
Administration cost	£5,295	£6,286	£991	£4,357	£5,172	£815
Monitoring costs	0	0	0	0	0	0
Consumables (incontinence pads for patients off SNM)	£301	£301	0	£990	£942	-£48
Adverse events (treatment and device costs)	£920 (338 + 582)	£995 (460 + 535)	£75	£1,177 (403 + 774)	£1,571 (645 + 926)	£394
Total	**£21,223**	**£27,261**	**£6,038**	**£19,812**	**£26,085**	**£6,273**

The base case results are provided as mean discounted cost (in £) per patient over 15 years horizon.

7.3.2 Sensitivity analysis results

The EAC created a tornado diagram from the company submission information for one-way sensitivity analysis, shown in figure 3, with the low and high values reported in table 13. This illustrates the importance of the replacement period for the stimulation devices. It should be noted that the submitted sensitivity analysis did not include any changes to costs, and that changes in discontinuation rates and adverse event rates were applied equally to both arms. All variations remained cost saving. Note that the tornado diagrams display the cost difference as calculated by the model, with negative numbers denoting a cost saving.

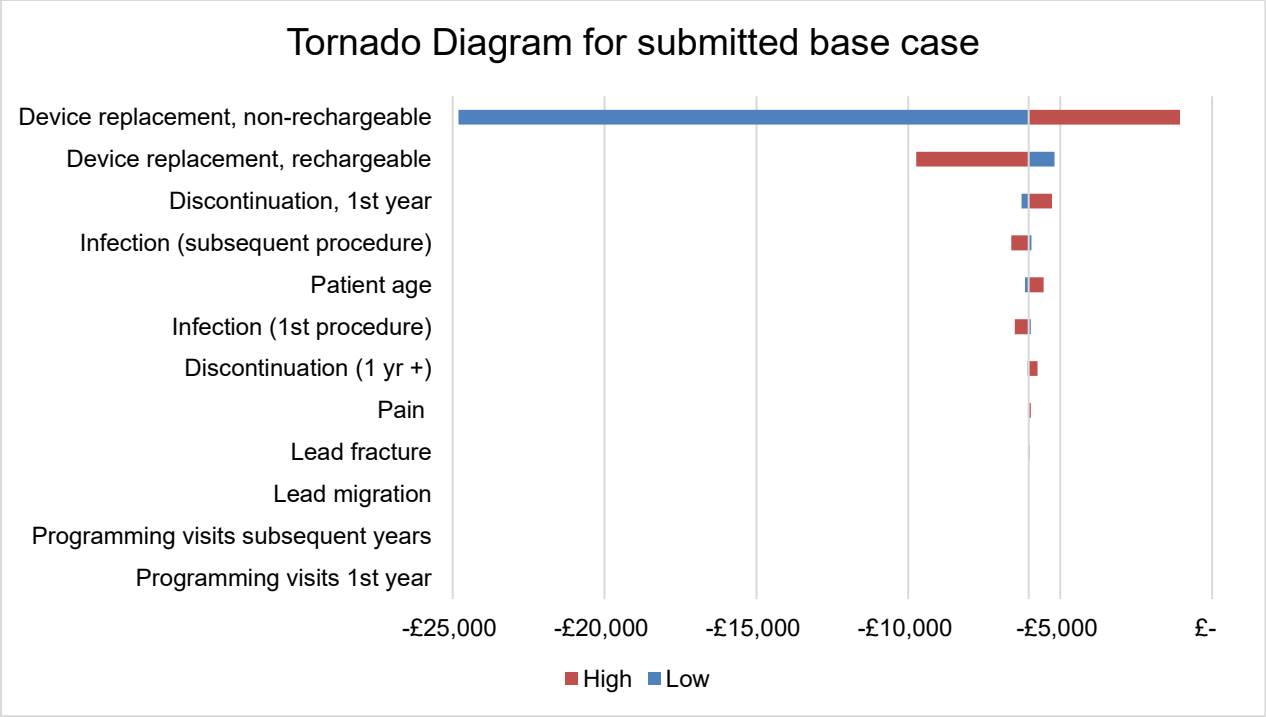

Figure 3. Tornado diagram of one-way sensitivity analyses.

Table 13. Values for one-way sensitivity analysis.

Scenario	Low	Cost saving	High	Cost saving	Absolute difference
Programming visits 1st year	1.0	£6,038	3.0	£6,038	£0
Programming visits subsequent years	1.0	£6,038	3.0	£6,038	£0
Lead migration	0.55%	£ 6,042	2.20%	£6,029	£13
Lead fracture	0.50%	£6,045	5%	£6,010	£36
Pain	2%	£6,061	10%	£5,971	£90
Discontinuation (1 yr +)	0.05%	£6,073	0.3	£5,745	£327
Infection (1st procedure)	2.20%	£5,966	19.10%	£6,497	£531
Patient age	43	£6,158	71	£5,543	£615

Scenario	Low	Cost saving	High	Cost saving	Absolute difference
Infection (subsequent procedure)	1.10%	£5,948	9.55%	£6,615	£667
Discontinuation, 1st year	0.56%	£6,271	3.36%	£5,276	£995
Device replacement, rechargeable	10.8 yrs	£5,188	19.2yrs	£9,746	£4,558
Device replacement, non-rechargeable	2.0 yrs	£24,814	7.0 yrs	£1,056	£23,758

The tornado diagram was repeated for the EAC base case, with the addition of device costs and varying each arm separately. In most cases the low/high range was unchanged, from the submitted analysis. For a few parameters that has significantly changed different ranges had to be chosen. These were largely an EAC assumption, as there was not available data. The parameters that cause the highest variation are the timing of required replacement devices and the device cost. It also highlights that where programing visit requirements are different for the two devices, this can impact on costs. As in the submitted model, all the analsyis remains cost saving throughout.

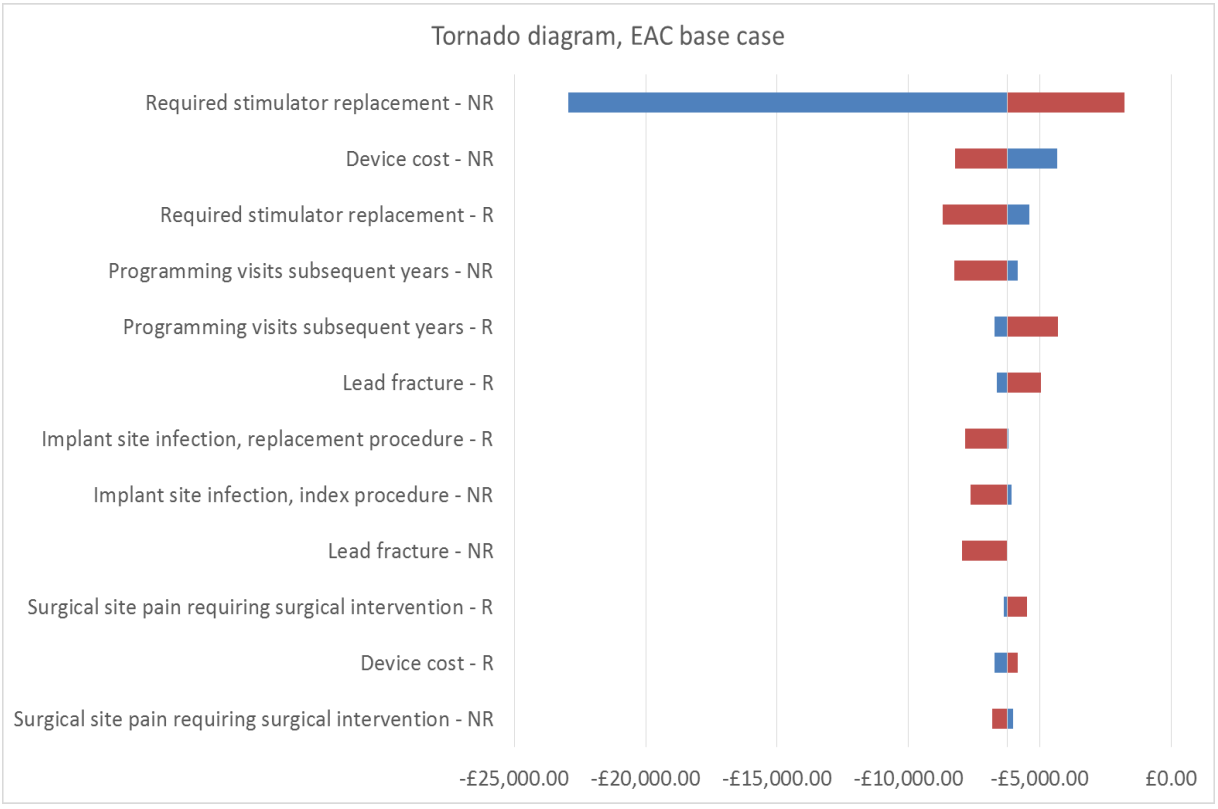

Figure 4. Revised tornado diagram, EAC base case.

The tornado diagram illustrates the parameters with the highest impact, table 14 shows all parameters that are varied, and the range of low/high values used (NR – non-rechargeable, R - rechargeable).

Table 14. Parameters varied in the revised tornado diagram.

Scenario	Low	Cost saving	High	Cost saving	Absolute difference
Therapy discontinuation (1yr+) - R	0.664%	£6,227	0.996%	£6,310	£83
Programming visits first year - R	1	£6,392	3	£6,183	£209
Therapy discontinuation (1st year) - R	0.56%	£6,349	3.36%	£6,140	£209
Programming visits first year - NR	1	£6,153	3	£6,364	£211
Lead migration/dislodgment - NR	0.14%	£6,102	0.55%	£6,603	£501
Therapy discontinuation (1yr+))- NR	0.664	£6,564	0.996	£6,005	£559
Lead migration/dislodgment - R	0.14%	£6,436	0.55%	£5,835	£601
Implant site infection, index procedure - R	0.50%	£6,307	10.00%	£5,667	£640
Implant site infection, replacement procedure - NR	1.10%	£6,189	9.55%	£6,838	£649
Therapy discontinuation, first year, per 3-month cycle - NR	0.56%	£6,428	3.36%	£5,778	£650
Patient age	43	£6,415	71	£5,723	£692
Surgical site pain requiring surgical intervention - NR	1%	£5,998	10%	£6,812	£814
Device cost - R	£5,600	£6,713	£8,400	£5,833	£880
Surgical site pain requiring surgical intervention - R	1%	£6,373	10%	£5,471	£902
Lead fracture - NR	0.13%	£6,520	1.27%	£7,947	£1,427
Implant site infection, index procedure - NR	2.20%	£6,063	19.10%	£7,618	£1,555
Implant site infection, replacement procedure - R	0.25%	£6,186	5.00%	£7,832	£1,646
Lead fracture - R	0.13%	£6,624	1.27%	£4,954	£1,670
Programming visits subsequent years - R	0.24	£6,707	3	£4,310	£2,397
Programming visits subsequent years - NR	0.24	£5,833	3	£8,263	£2,430
Required stimulator replacement - R	10.8	£5,381	19.2	£8,696	£3,315

Device cost - NR	£4,896	£4,334	£7,344	£8,212	£3,878
Required stimulator replacement - NR	2.0 yrs	£22,935	7.0 yrs	£1,782	£21,153

The impact of varying the expected time until replacement of the Axonics device is shown in the threshold diagram, figure 5. The uneven shape of the line is because the cost difference is very largely dependent on the number of replacement devices required, which does not occur evenly over the 15 year time horizon (e.g. a 4 and 5 year device life will require 3 replacements, a 6 year device life requires 2 replacements).

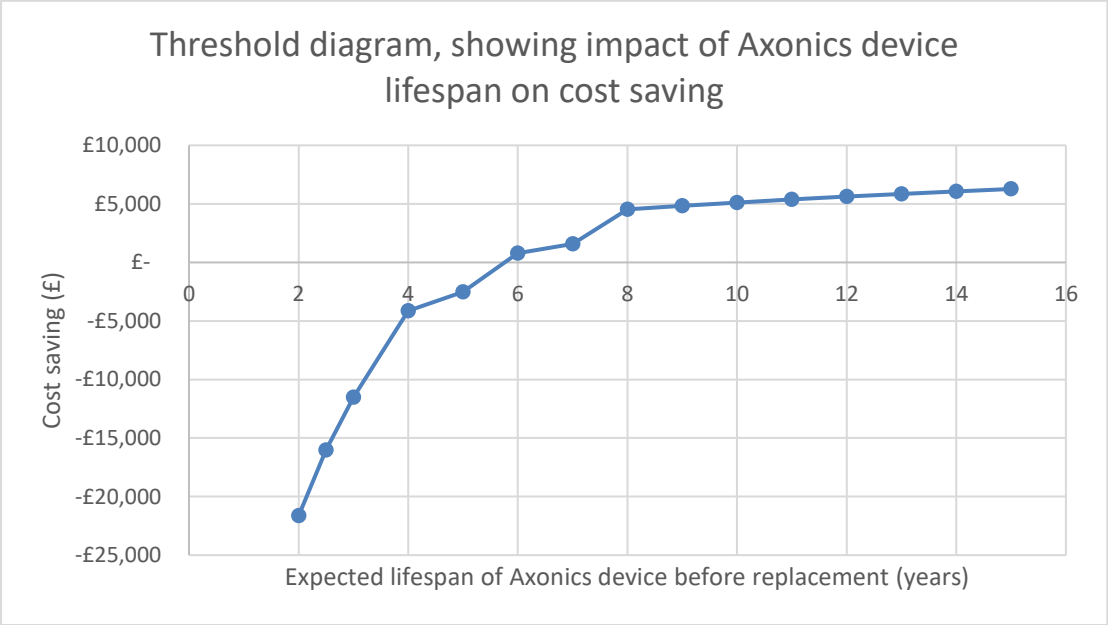

Figure 5. Threshold diagram

Figure 5 shows that Axonics becomes cost saving in the EAC base case, when the device lifetime prior to replacement is just under 6 years.

A two way sensitivity analysis was carried out by both the company and the EAC, changing both Axonics and the comparator device lifetimes. Table 15 gives the results for the EAC base case. The shaded areas are where Axonics is cost incurring.

Table 15. Expected lifetimes for devices.

Expected lifetime of comparator (years)		Expected lifetime for Axonics rechargeable device (years)						
		2.0	**5.0**	**7.0**	**9.0**	**11.0**	**13.0**	**15.0**
	2.0	-£4,980	£14,156	£18,249	£21,498	£22,043	£22,518	£22,935
	3.0	-£14,208	£4,929	£9,022	£12,270	£12,815	£13,290	£13,707
	4.0	-£20,925	-£1,788	£2,304	£5,553	£6,098	£6,573	£6,990
	4.4	-£21,642	-£2,506	£1,587	£4,836	£5,381	£5,856	**£6,273**
	5.0	-£22,406	-£3,270	£823	£4,072	£4,617	£5,092	£5,509
	6.0	-£25,413	-£6,276	-£2,183	£1,065	£1,610	£2,085	£2,502
	7.0	-£26,133	-£6,997	-£2,904	£345	£890	£1,365	£1,782

7.3.3 Additional results

The scenarios from both the company and EAC are presented below in table 16. In all cases these are calculated using the EAC base case.

It can be seen that a 10 year time horizon is actually slightly more cost saving, as 3 comparator devices have been used, and only the initial Axonics device. At 15 years, 4 comparator devices and 2 Axonics devices have been used.

As the time horizon increases, the cost saving also increases. With increasing years fewer patients remain in the model (due to mortality) and the cost saving starts to plateau.

Initial testing before device implantation to test patients for device effectiveness is described in detail in Appendix G. Within the UK NHS pathway this will happen in both arms (and is therefore not modelled in the base case). The reduction in cost saving in this scenario is because some patients are non-responders, and do not proceed to receive either device.

Because the reduction in adverse events for subsequent procedures is an assumption, the EAC tested this in a scenario where both pain and infection rates were the same for every procedure. As expected the cost savings increased slightly, since the comparator device has more procedures and so it benefited from this assumption.

Finally, although the EAC base case used data from InterStim studies for the comparator, and data from Axonics studies for the intervention, we also investigated other scenarios. The use of InterStim study data for both arms is as submitted by the company, but including the EAC corrections and modifications. The changes introduced by the EAC modelling work prior to introducing Axonics data reduced the cost saving from £6,273 to £5,816.

Table 16. Results from scenario analysis.

Scenarios	Axonics	Comparator	Cost saving
EAC Base Case	**£19,812**	**£26,085**	**£6,273**
10 year time horizon	£15,937	£22,244	£6,307
20 year time horizon	£20,677	£28,684	£8,007
25 year time horizon	£21,571	£30,584	£9,014
30 year time horizon	£22,604	£31,819	£9,215
Including testing	£17,049	£21,325	£4,275
Added by EAC			
Increased time horizon to 40 years	£32,734	£22,932	£9,802
No change in probability of pain or infection for subsequent procedures	£19,827	£26,347	£6,520
InterStim data used for both arms	£20,264	£26,080	£5,816
Axonics data used for both arms	£19,812	£25,469	£5,657
Post Fact check update on resources following additional information from company (table 17) and error correction.	£19,695	£26,041	-£**6,345**

None of the scenarios resulted in Axonics becoming cost incurring, and the overall differences were small.

During fact check the company identified differences between the model and their expected use of components. The EAC have added an additional scenario, with the EAC base case amended to reflect this information. Table 17 shows the updated resource use as listed by the company. In addition the EAC identified an error in the model that referenced a cell incorrectly for revisions due to pain. The correction of this error made less than £1 difference to the outcome. Overall the update has a small impact on the model outcomes.

Table 17: Submitted by company during Fact Check.

	Tined Lead (TL) Introducer Kit	Implanted Pulse Generator (IPG)	Tined leads (TL)	Charger	Percutaneous Nerve Evaluation (PNE) KIT	Trial Stimulator	Tined Leads (TL) extension	Patient remote control
Testing	✓		✓		✓	✓	●	✓
Initial implant procedure	✓	✓	✓	●				✓
Replacement due to infection	✓	✓	✓					
Replacement due to pain	✓	✓	✓					
Replacement due to battery depletion		✓						
Lead revision	✓		✓					
Lead replacement	✓		✓					
Required replacement of Charger System at 7.5 years				●				
Required replacement of Patient Remote at 7.5 years								✓
✓ required for both devices; ● required for rechargeable device only								

7.4 EAC Interpretation of economic evidence

The EAC made some corrections to calculations and added some alternative parameters, as well as sensitivity analysis and additional scenarios. These are described fully in the previous sections, however the changes in the EAC base case are summarised here.

Corrections to calculations:

- Inflation calculation using index table
- Cumulative discontinuation correction
- Calculation of VAT for comparator device costs
- Update of comparator cost from NHS Supply chain

Additional EAC work:

- Use day case costs for the initial procedure, rather than inpatient
- Allow lead migration / dislocation / fracture throughout the entire model duration, rather than the initial cycle only
- Interpretation of Chughtai et al (2015) to give a higher discontinuation rate.

- Introduction of data from ARTISAN and RELAX studies for Axonics clinical parameters

Although the EAC made several changes and carried out additional sensitivity analysis, the model remained cost saving and the cost difference between the two arms did not vary greatly. This leads us to believe that, if the assumptions inherent in the model are accepted, the rechargeable Axonics device is cost saving compared to a non-rechargeable device.

8 Conclusions

8.1 Conclusions on the clinical evidence

All papers relevant to assessment of the Axonics device are derived from 2 observational, single-arm studies. The RELAX-OAB and ARTISAN-SNM studies add weight to the existing body of evidence that SNM devices are a useful treatment option in people with refractory OAB. The populations, intervention, and outcome measures are relevant to the decision problem, but the lack of statistically comparative data and long-term clinical findings are substantial limitations. Findings from subgroups are reported, but represent relatively small numbers of individuals. There are a number of uncertainties relating to the existing clinical evidence, and cautious interpretation is advised.

The single-arm “before and after” designs are not able to demonstrate superior clinical effectiveness outcomes of the Axonics device over competing technologies. However the unique advantage of the Axonics system lies in its potential extended battery life, and the avoidance of multiple surgeries with their associated safety risks.

Given that the Axonics system only received regulatory approvals in 2016, the full lifespan of the rechargeable IPG battery and associated long-term clinical outcomes have not yet been proven. Bench testing of repeated charge/discharge cycles suggests that each battery will provide sufficient power to last more than 15 years; NICE has commissioned a separate technical exercise to assess the reliability of this supporting data. Assuming battery test data provide a robust estimate, this assessment places a greater emphasis on projected economic evidence.

8.2 Conclusions on the economic evidence

The model compares a rechargeable to non-rechargeable SNM device at a time horizon of 15 years. There is an assumption that both devices sit at the same point in the UK NHS clinical pathway, and that they both have equal clinical effectiveness. Although there is no comparative data, the EAC have

not identified any evidence to indicate that this is not a reasonable assumption.

The model is strongly driven by the expected device lifetimes and device costs. The Axonics device is slightly more expensive than the non-rechargeable comparator, but this is offset by the longer expected duration of the device.

The EAC made some amendments to the model and carried out additional sensitivity analysis. Throughout these changes the model remained consistently cost saving, and the variation in cost saving was relatively small. This leads us to conclude that the model is robust, and that given the device costs and expected device lifetimes, the Axonics rechargeable device is cost saving compared to the non-rechargeable comparator.

9 Summary of the combined clinical and economic sections

All clinical evidence relating to the Axonics technology originates from 2 single-arm studies. Limitations of both study designs and reporting are indicative of low quality evidence, and the EAC was not able to assess comparative effectiveness against alternative SNM systems. Follow-up is limited to a maximum of 2 years, so it has not been possible to verify long-term safety or clinical effectiveness. Comparisons between baseline measures and follow-up up to 1 year (ARTISAN-SNM study) and 2 years (RELAX-OAB) show reductions in symptoms of UUI and UF, and improvements in condition-specific quality of life. There were low numbers of device explantations and procedure-related wound infections, and no unexpected device-related AEs. A key assumption for the economic model is that both devices sit at the same point in the UK NHS clinical pathway, and that they both have equal clinical effectiveness. Given this assumption, the use of Axonics rechargeable device remained cost saving when compared to a non-rechargeable device, despite several EAC amendments and sensitivity testing. The model is strongly driven by the expected device lifetimes and device costs. The Axonics device is slightly more expensive than the non-rechargeable comparator, but this is offset by the longer expected lifetime of the rechargeable device.

10 Implications for research

Research is recommended to address key uncertainties in the evidence base. Long-term clinical effectiveness (battery life) outcomes would be of particular interest. Ideally, randomised controlled trials should be carried out to mitigate risks associated with potential bias. Indirect comparisons between dissimilar populations are unlikely to add value.

11 References

Blok, B. et al. 2018a. Three month clinical results with a rechargeable sacral neuromodulation system for the treatment of overactive bladder. Neurourology & Urodynamics 37(S2), pp. S9-S16.

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Blok, B. et al. 2019b. International Continence Society abstract #158 available at: https://www.ics.org/2019/abstract/158 [accessed 5/11/2019)

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Coyne, K. et al. 2006. Determining the importance of change in the overactive bladder questionnaire. The Journal of Urology 176(2), pp. 627-632.

Kiefer, C. et al. 2015. Indirect comparisons and network meta-analyses. Deutsches Ärzteblatt International 112(47), pp. 803-808.

Lane, F. et al. 2020. Unpublished abstract and conference poster.

Marcelissen, T. et al. 2018. Management of idiopathic overactive bladder syndrome: What is the optimal strategy after failure of conservative treatment? European Urology Focus 4(5), pp. 760-767.

McCrery, R. et al. 2019. Treatment of urinary urgency incontinence using a rechargeable SNM system: 6-month results of the ARTISAN-SNM study. Journal of Urology, p. 101097JU0000000000000458.

12 Appendices

Appendix	Title
A	Literature searches
B	EAC critical appraisal tables (clinical evidence)
C	Flow diagram with details of subgroup calculations (RELAX-OAB)
D	Quality appraisal of economic evidence
E	Stress test performed on the model submitted by the company
F	Additional costing results
G	Testing prior to implant

12.1 Appendix A- Literature searches

Company search strategy and study selection for clinical evidence

A literature search was performed using the PubMed database to identify published evidence on sacral neuromodulation systems. The search strategy is provided below. The search was performed to include all articles up to 31st July 2019. Published and unpublished evidence on sacral neuromodulation was analysed. Specific clinical evidence on the sponsor's technology of rechargeable sacral neuromodulation was included, as well as evidence on other sacral neuromodulation systems. A single comparator was identified in the literature: the non-rechargeable InterStim® SNM system from Medtronic (referenced as "InterStim" further in the text).

A total of 11 published articles were used for the evaluation. Four articles were on the sponsor's technology (the Axonics SNM System), and the remaining seven (7) articles were on comparative technology InterStim. A grey search was carried out to include conference presentations, abstracts and unpublished manuscripts on the sponsor's technology. Unpublished data is only used for the sponsor's technology. For comparator clinical evidence, only peer-reviewed, published evidence was considered appropriate.

The Entrez PubMed/Medline database was used to perform a search of published investigational clinical data. The specific search term combinations used for conducting the literature search are listed below.

Table 1: Literature search results

Search ID	Search Terms	PubMed (up to 31 July 2019)
1	Interstim sacral modulation [any field] [English + Humans]	5
2	Interstim neuromodulation [any field] [English + Humans]	78
3	Interstim Neurostimulator [any field] [English + Humans]	13
4	Medtronic sacral modulation [any field] [English + Humans]	4
5	Medtronic neuromodulation [any field] [English + Humans]	122

Search ID	Search Terms	PubMed (up to 31 July 2019)
6	Medtronic neurostimulator [any field] [English + Humans]	26
7	Interstim urinary [any field] [English + Humans]	91
8	Interstim bowel [any field] [English + Humans]	14
9	Interstim incontinence [any field] [English + Humans]	77
10	Interstim model 3058 [any field] [English + Humans]	0
11	Interstim model 3023 [any field] [English + Humans]	0
12	Interstim urinary retention [any field] [English + Humans]	34
13	Interstim overactive bladder [any field] [English + Humans]	26
14	Interstim urinary urge [any field] [English + Humans]	33
15	Interstim fecal [any field] [English + Humans]	23
16	Interstim fecal incontinence [any field] [English + Humans]	23
17	Interstim bowel control [any field] [English + Humans]	2
18	Sacral Nerve stimulation fecal incontinence [any field] [English + Humans]	396
19	Sacral Nerve stimulation urinary incontinence [any field] [English + Humans]	312
20	Sacral neuromodulation fecal incontinence [any field] [English + Humans]	164
21	Sacral neuromodulation urinary incontinence [any field] [English + Humans]	290
22	Rechargeable AND sacral AND (neuromodulation OR stimulation OR neurostimulation)	14
	Subtotal of literature search results	**1747**
	Duplicates	801
	Unique results from literature search	946
	Exclusions applied (see details below)	937
	Articles included	9
	Additional Articles (latest follow-up.)	2
	Total Articles included from literature	**11**
	RELEVANT	**11**
	Exclusions applied**	
	Duplicate/Duplicate Data Set	801
	>15 yrs, non-RCT	1
	Animal data	3
	Case report/series	38
	Cost assessment	20
	Dissimilar device	161
	Dissimilar disease state	17
	Dissimilar indication	77
	Dissimilar medical area	7
	Dissimilar patient population	64
	Dissimilar technique	1
	Intra-device comparison	2

Search ID	Search Terms	PubMed (up to 31 July 2019)
	Latest article included	1
	N<100, >15yrs	83
	N<100, non-RCT	42
	No abstract	53
	No author	4
	No clinical data/outcome	105
	No device evaluation/no device identification	32
	Patient care management/clinical practice	6
	Patient physiology/anatomy	30
	Study type	124
	Technical note/clinical technique	66

*****Database search contains the following limiters: "human study subjects", "English language", "clinical trials".

Company Inclusion/Exclusion Criteria

Inclusion Criteria

- Articles where study subject population is overactive bladder (OAB), including urinary incontinence, urgency urinary incontinence and urinary frequency
- Human randomized controlled clinical trials
- Peer-reviewed journal publications, or equivalent
- Methods section clearly indicates that the InterStim System was the subject of the study
- Follow-up outcome data included evaluations of mortality, morbidity and/or clinical success

Exclusion Criteria

- Articles where study subject population has pre-dominantly stress incontinence
- Articles >15 years old
- Studies with N < 100 (non-randomized; greater than 15 yr; except for Sponsor studies)
- Dissimilar patient populations (e.g. pediatric, first-treatment, Asian-only populations, etc.)
- Duplicate publications (e.g. identical individual citations and/or identical citations within meta-analysis/systematic review included for review)
- No long-term follow-up data for safety / efficacy

- Dissimilar device (e.g. tibial nerve stimulation, spinal cord stimulation)
- Animal trials (small or large); Case Reports
- Retrospective case series ; Review or meta-analysis articles
- Technical notes ; Bench/anatomical model reports
- Book chapters, abstracts, scientific presentations, single case reports, white papers and other monographs not published in peer-reviewed journals
- Random experience and reports lacking sufficient detail to permit scientific evaluation
- Unsubstantiated opinions and lack of statistical design (patient population does not support statistical significance)
- Medicinal substance focus as patient population is refractory (resistant to medication)
- Foreign language only articles (not available in English)
- Studies of clinician specific technique(s) not reflecting state of the art
- Study focus on disease state evaluation (e.g. progression of healthy eyes, physiological/anatomical states, etc.)
- Intra-device comparative studies
- Studies with publication dates outside specified limits
- Technical studies, or those where non-standard SNM parameters were used or where other forms of sacral neuromodulation (e.g. transcutaneous) are employed
- Indications outside those of the Axonics SNM System (e.g. non-chronic fecal incontinence, obstructive urinary retention, FI secondary to organic pathologies)
- Lack of information on elementary aspects (author, study methods, number of patients, adverse events, clinical outcomes)
- Conclusions not aligned with study results
- Illegal activities

EAC search strategy and study selection for clinical and economic evidence

The EAC conducted a single search for both clinical and economic evidence as directed by the scope. Ten bibliographic databases and 2 clinical trial registries were searched using a range of free text terms and subject headings, see below for databases, search strategies and search results. The MHRA's medical device alerts and field safety notices were also searched for adverse events.

Date	**Database Name**	**Total Number of records retrieved**	**Total number of records from**

			database after de-duplication
21/08/19	Cochrane Library CDSR CENTRAL	12	
21/08/19	CRD DARE HTA NHS EED	4	
21/08/19	EMBASE	58	
21/08/19	Medline (ALL – includes Medline In Process & Medline Epub Ahead of Print)	79	
21/08/19	PubMed	9	
21/08/19	Scopus	72	
21/08/19	Web of Science	12	146
04/09/19	MHRA – search of MDA & FSN	0	
04/09/19	Clinicaltrials.gov	2	
04/09/19	ICTRP	2 (duplicates)	
04/09/19	Records from manufacturer	No additional studies	
			144
			144 and 2 clinical trials

Database Search strategies

Cochrane Library (CDSR and CENTRAL)

ID Search Hits

#1 MeSH descriptor: [Urinary Bladder, Overactive] this term only 592

#2 MeSH descriptor: [Urinary Incontinence] this term only 1147

#3 MeSH descriptor: [Urinary Incontinence, Urge] this term only 161

#4 ("urinary incontinence"):ti,ab,kw OR ("urinary urge* incontinence"):ti,ab,kw OR ("overactive bladder"):ti,ab,kw OR ("refractory OAB"):ti,ab,kw (Word variations have been searched) 6786

#5 #1 OR #2 OR #3 OR #4 6845

#6 MeSH descriptor: [Sacrum] this term only and with qualifier(s): [innervation - IR] 13

#7 MeSH descriptor: [Implantable Neurostimulators] explode all trees 177

#8 (axonics):ti,ab,kw (Word variations have been searched) 817

#9 ("rechargeable Sacral Neuromodulation"):ti,ab,kw (Word variations have been searched) 1

#10 #6 OR #7 OR #8 OR #9 1007

#11 #5 AND #10 12

CRD – DARE, NHS EED and HTA

overactive bladder AND neuromodulation

2010 to 2019

Results = 4

Database: EMBASE <1947-Present>

1 overactive bladder/ (15335)

2 urine incontinence/ or urge incontinence/ (51684)

3 ("urinary incontinence" or "urinary urge* incontinence").tw. (37191)

4 "overactive bladder".tw. (10476)

5 "refractory OAB".tw. (264)

6 1 or 2 or 3 or 4 or 5 (75138)

7 implantable neurostimulator/ (684)

8 axonics.tw. (13)

9 "rechargeable Sacral Neuromodulation".tw. (12)

10 7 or 8 or 9 (701)

11 6 and 10 (60)

12 limit 11 to (english language and yr="2010 -Current") (58)

Database: Ovid MEDLINE(R) ALL <1946 to August 20, 2019>

1 Urinary Bladder, Overactive/ (4265)

2 Urinary Incontinence/ or Urinary Incontinence, Urge/ (22329)

3 ("urinary incontinence" or "urinary urge* incontinence").tw. (22690)

4 "overactive bladder".tw. (5711)

5 "refractory OAB".tw. (85)

6 1 or 2 or 3 or 4 or 5 (39595)

7 Sacrum/ir [Innervation] (297)

8 Implantable Neurostimulators/ (518)

9 axonics.tw. (7)

10 "rechargeable Sacral Neuromodulation".tw. (7)

11 7 or 8 or 9 or 10 (813)

12 6 and 11 (104)

13 limit 12 to yr="2010 -Current" (84)

14 limit 13 to english language (79)

Pubmed

Axonics OR “rechargeable sacral neuromodulation”

Results = 9

Scopus

(TITLE-ABS-KEY ("overactive bladder" OR "urin* incontinence" OR "urin* urge* incontinence" OR "refractory OAB") AND TITLE-ABS-KEY ("implantable neurostimulator" OR "axonics" OR "rechargeable Sacral Neuromodulation")) AND PUBYEAR > 2009

Results = 72

Web of Science

TOPIC: ("overactive bladder" OR "urin* incontinence" OR "urin* urge* incontinence" OR "refractory OAB") AND TOPIC: ("implantable neurostimulator" OR "axonics" OR "rechargeable Sacral Neuromodulation")
Indexes=SCI-EXPANDED, CPCI-S Timespan=2010-2019

Results = 12

Clinicaltrials.gov

Searched for: Axonics OR (sacral neuromodulation AND (Incontinence, Urinary OR overactive bladder OR Incontinence, Urge))

Results = 2

ICTRP

Searched for: Axonics

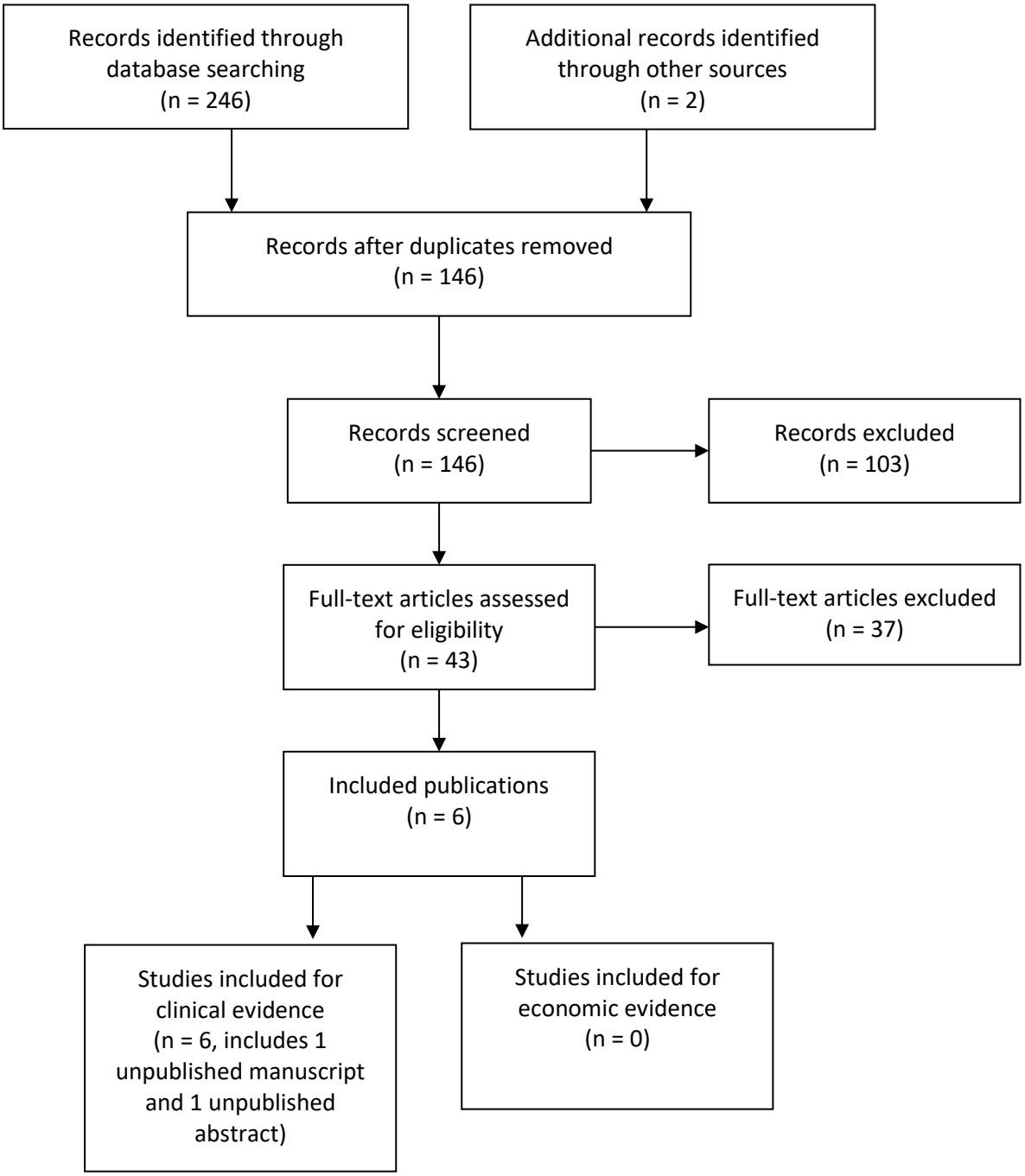
Results = 2 (duplicates of Clinicaltrials.gov)

MHRA

Searched for: sacral neuromodulation OR axonics

Results = 0

EAC Study Selection



Company Search strategy for economic evidence

The search for economic evaluations was performed in August 2019, using a combination of searches in Embase, Medline/Pre-Medline, Health Technology Assessment Database, and NHS Economic Evaluation Database. The searches were designed to include all economic studies of sacral nerve stimulation for overactive bladder.

EMBASE SEARCH

- **Database:** Embase Classic+Embase 1967 (plus <1966) to August 2019
- **Limits:** none
- **Search Date:** August 22, 2019
- **Search Terms and Strategy:**

#	Searches	Results
1	'health economics'/exp OR 'health economics' OR 'economic evaluation' OR 'health care cost' OR pharmacoeconomics OR econom* OR pharmacoeconomic* OR 'cost effectiveness analysis' OR 'cost utility analysis' OR 'cost minimization analysis' OR 'cost benefit analysis' OR ('cost benefit' AND analysis) OR (budget AND impact AND analysis) OR 'cost effective*'	1,451,265
2	'overactive bladder'	16,780
3	'urge incontinence'	7,888
4	urgency AND incontinence	9,680
5	'urinary urgency'	6,870
6	urge AND 'incontinence'	9,451
7	#2 OR #3 OR #4 OR #5 OR #6	30,373
8	#1 AND #7	1,810
9	(bladder* (overactiv* or over activ* or over-activ* or instabilit* or hyper-reflex* or hyperreflex* or hyper reflex* or incontinen*))	36,967
10	detrusor* AND ((overactiv* OR over) AND activ* OR 'over activ*' OR instabilit* OR 'hyper reflex*' OR hyperreflex* OR hyper) AND reflex*	7,511
11	#7 OR #9 OR #10	53,738
12	#1 AND #11	2,483
13	'neuromodulation'	48,260
14	'sacral nerve stimulation'	2,965
15	'sacral nerve stimulator'	210
16	sacral AND neuro AND modulation	36
17	sacral AND neuro AND modulator	0
18	sacral AND neuro AND stimulation	172
19	sacral AND neuro AND stimulator	25
20	sacral AND modulation	401
21	sacral AND modulator	17
22	sacral AND stimulation	5,012
23	sacral AND stimulator	792
24	neuro AND modulation	3,545
25	neuro AND modulator	503

26	neuro AND stimulation	9,905
27	neuro AND stimulator	437
28	nerve AND modulation	45,550
29	nerve AND modulator	4,842
30	nerve AND stimulation	195,693
31	nerve AND stimulator	8,803
32	'devices'	660,446
33	'medical device'	58670
34	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32	948,542
35	#11 AND #34	5,673
36	#1 AND #35	437

MEDLINE SEARCH

- **Databases:** PubMed/Medline/Pre-Medline 1946 to August 2019
- **Limits/Filters**:
  - Publication type: NOT letter, editorial, or historical article
  - Species: not animal or mixed study
- **Search Date:** August 22, 2019
- **Search Terms and Strategy:**

#	Searches	Results
1	"Economics"[Mesh:NoExp] OR "Costs and Cost Analysis"[Mesh] OR "Economics, Hospital"[Mesh] OR "Economics, Medical"[Mesh:NoExp] OR "Economics, Nursing"[Mesh] OR "Economics, Pharmaceutical"[Mesh] OR economic*[tiab] or cost[tiab] or costs[tiab] or costly[tiab] or costing[tiab] or price[tiab] or prices[tiab] or pricing[tiab] or pharmacoeconomic*[tiab] OR (expenditure*[tiab] not energy[tiab]) OR "value for money"[tiab] OR budget*[tiab] NOT ("energy cost"[Title/Abstract] OR "oxygen cost"[tiab] OR "metabolic cost"[tiab] OR energy expenditure[tiab] OR "oxygen expenditure"[tiab] OR (letter[pt] OR editorial[pt] OR historical article[pt]) OR animals[mesh:noexp])	766,040
2	"Urinary Incontinence, Urge"[Mesh]	875
3	"Urinary Bladder, Overactive"[Mesh]	4,269
4	"Urinary Bladder"[Mesh] OR "urinary"[tiab] OR "urine"[tiab] "bladder"[tiab] OR void*[tiab]	105,951
5	"urge"[tiab] OR "urgency"[tiab]	23,301
6	"Urinary Incontinence"[Mesh] OR "Urinary Incontinence"[tiab] OR "incontinence"[tiab] OR "incontinent*"[tiab]	55,319
7	#4 AND #5	4,898
8	#5 AND #6	6,609
9	"detrusor"[tiab] AND ("over active"[tiab] OR "over activity"[tiab] OR "over-active"[tiab] OR "over-activity"[tiab] OR "overactive"[tiab] OR "overactivity"[tiab] OR contract*[tiab] OR uninhibit*[tiab] OR involuntary*[tiab])	5,852
10	#2 OR #3 OR #7 OR #8 OR #9	14,991
11	#1 AND #10	514
12	"Implantable Neurostimulators"[MeSH]	10,499

13	sacrum[tiab] or sacral[tiab]	19,932
14	nerve[tiab] OR neurost*[tiab] OR neuromo*[tiab] OR stimulat*[tiab] OR modulat*[tiab]	1,949,416
15	#13 AND #14	4,784
16	"Prostheses and Implants"[MeSH]	496,695
17	"Electrodes, Implanted"[MeSH]	44,006
18	"Implants, Experimental"[MeSH]	3,251
19	device*[tiab]	387,161
20	implant*[tiab]	381,279
21	#16 OR #17 OR #18 OR #19 OR #20	1,039,122
22	#15 OR #21	1,042,612
23	#10 AND #22	1,781
24	#1 AND #23	101

HEALTH TECHNOLOGY ASSESSMENT DATABASE SEARCH

- **Database:** University of York, Centre for Reviews and Dissemination, Health Technology Assessment Database
- **Limits:** none
- **Search Date:** August 22, 2019
- **Search Terms and Strategy:**

#	Searches	Results
1	MeSH descriptor: [Urinary Incontinence] this term only	0
2	MeSH descriptor: [Urinary Incontinence, Urge] this term only	51
3	MeSH descriptor: [Urinary Bladder, Overactive] this term only	10
4	(bladder*):TI OR (detrusor*):TI OR (urin*):TI	201
5	(urge*):TI OR (incont*):TI	131
6	(overact*):TI OR (over-act*):TI OR (over act*):TI	12
7	(hyperreflex*):TI OR (hyper-reflex*):TI OR (hyper reflex*):TI	0
8	(contract*):TI OR (uninhibit*):TI OR (involuntary*):TI	23
9	#1 OR #2 OR #3	58
10	#4 AND #5	71
11	#4 AND #6	2
12	#4 AND #7	0
13	#4 AND #8	0
14	#5 AND #6	2
15	#5 AND #7	0
16	#5 AND #8	0
17	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	90
18	MeSH descriptor: ["Implantable Neurostimulators"] this term only	0
19	MeSH descriptor: ["Prostheses and Implants"] this term only	0
20	MeSH descriptor: ["Electrodes, Implanted"] this term only	0
21	MeSH descriptor: ["Implants, Experimental"] this term only	0
22	(sacrum):TI OR (scaral):TI	0
23	(nerve*):TI OR (neuro*):TI	337
24	(stimulat*):TI OR (modulat*):TI	283
25	(neurostimulat*):TI OR (neuromodulat*):TI	24
26	(device*):TI OR (implant*):TI	564

27	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	1,080
28	#17 AND #27	21

NHS ECONOMIC EVALUATION SEARCH

- **Database:** University of York, Centre for Reviews and Dissemination, NHS Economic Evaluation (NHS EE) Database
- **Limits:** none
- **Search Date:** August 22, 2019
- **Search Terms and Strategy:**

#	Searches	Results
1	MeSH descriptor: [Urinary Incontinence] this term only	31
2	MeSH descriptor: [Urinary Incontinence, Urge] this term only	6
3	MeSH descriptor: [Urinary Bladder, Overactive] this term only	27
4	(bladder*):TI OR (detrusor*):TI OR (urin*):TI	198
5	(urge*):TI OR (incont*):TI	64
6	(overact*):TI OR (over-act*):TI OR (over act*):TI	32
7	(hyperreflex*):TI OR (hyper-reflex*):TI OR (hyper reflex*):TI	0
8	(contract*):TI OR (uninhibit*):TI OR (involuntary*):TI	13
9	#1 OR #2 OR #3	59
10	#4 AND #5	33
11	#4 AND #6	32
12	#4 AND #7	0
13	#4 AND #8	0
14	#5 AND #6	2
15	#5 AND #7	0
16	#5 AND #8	0
17	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	80
18	MeSH descriptor: ["Implantable Neurostimulators"] this term only	0
19	MeSH descriptor: ["Prostheses and Implants"] this term only	0
20	MeSH descriptor: ["Electrodes, Implanted"] this term only	0
21	MeSH descriptor: ["Implants, Experimental"] this term only	0
22	(sacrum):TI OR (scaral):TI	0
23	(nerve*):TI OR (neuro*):TI	155
24	(stimulat*):TI OR (modulat*):TI	153
25	(neurostimulat*):TI OR (neuromodulat*):TI	10
26	(device*):TI OR (implant*):TI	289
27	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	571
28	#17 AND #27	16

Inclusion criteria:

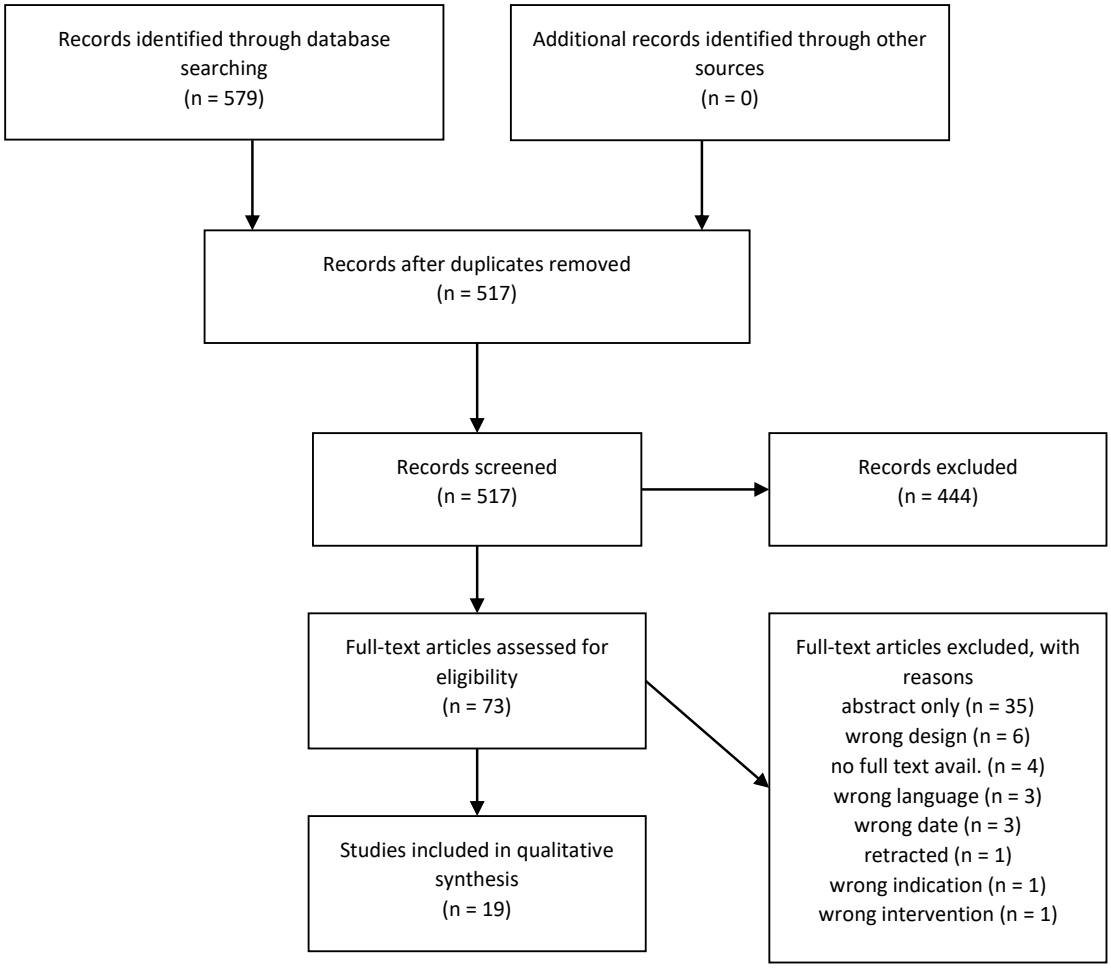
- English-language full-text publications
- Studies published between 2000 up until August 22, 2019
- Studies in patients with overactive bladder, defined as urge or urge incontinence, for whom pharmaceutical treatment was not effective or not effective enough or who were not candidates for those
- Studies reporting on sacral neuromodulation

- Some form of comparator, e.g., another neuromodulation implantable device
- Economic evaluations:
    - Cost-utility analyses (CUAs)
    - Cost-effectiveness analyses (CEAs) with an effectiveness measure other than utility
    - Cost-benefit analyses (CBAs)
    - Budget impact analyses
    - Cost minimization analyses (CMA)

Exclusion criteria:

- Studies that only included patients with stress or overflow incontinence
- Abstracts/conference proceedings who were not subsequently published as a full text
- Commentary/editorials/opinion pieces
- Letters including research
- Review articles, including systematic reviews
- Papers that only described a study design but did not report results
- Studies that reported only on resource use or cost components but not the full treatment

Study Selection


Records identified through database searching
(n = 579)
Additional records identified through other sources
(n = 0)
Records after duplicates removed
(n = 517)
Records screened
(n = 517)
Records excluded
(n = 444)
Full-text articles assessed for eligibility
(n = 73)
Full-text articles excluded, with reasons
abstract only (n = 35)
wrong design (n = 6)
no full text avail. (n = 4)
wrong language (n = 3)
wrong date (n = 3)
retracted (n = 1)
wrong indication (n = 1)
wrong intervention (n = 1)
Studies included in qualitative synthesis
(n = 19)

12.2 Appendix B – EAC critical appraisal of clinical evidence

Checklist adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence - 12 questions to help you make sense of a cohort study.

Study name: ARTISAN-SNM, McCrery (2019)		
Study question	**Response**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Not clear	Prospective study with informed consent. Not clear whether recruitment was consecutive. Study was funded by the company. Sample size requirement was met (n = 116).
Was the exposure accurately measured to minimise bias?	Yes	All eligible patients received the same implant. A single-stage procedure was used, unlike standard care where an external test is first carried out.
Was the outcome accurately measured to minimise bias?	Yes	Primary outcome measure: Responder rate (≥ 50% reduction in UUI episodes per day) at 6 months. Baseline 72-hour (3 day) voiding diary was compared with follow-up data.
Have the authors identified all important confounding factors?	Yes	Reported: 40/129 (31%) of the same were taking concomitant medication to treat the condition; at least 17 individuals had previous surgical treatment Excluded: neurological conditions, stress incontinence, UTI, recent treatments with botulinum toxin or tibial nerve stimulation, mechanical obstruction, pelvic cancer, interstitial cystitis/bladder pain syndrome, recent (4 weeks) changes to current medication.
Have the authors taken account of the confounding factors in the design and/or analysis?	Not clear	Only 2/129 participants (2%) were male. The authors claim this is representative of the UUI population. Expert advisers to NICE estimate that 80% of the OAB/UUI population are typically female.
Was the follow-up of patients complete?	Partially	For “a majority of” questionnaires, patients with missing data at follow-up were still included using their baseline data. Key results were based on ITT analyses. **At 6 months**, 3 participants had exited the study– 1 died (unrelated), 2 explanted (1 due to wound infection, 1 due to ‘unrelated’ pain). No patients were lost to follow-up in the first 6 months. **At 1-year [unpublished abstract],** 2 devices had been explanted due to lack of efficacy, 1 device was explanted and 1 lead migration resulted in lead revision surgery. There is no mention of the device previously explanted due to ‘unrelated’ pain (unless it had been reclassified as ‘lacking efficacy’). The study is designed to follow participants for 2 years, but primary outcome data was analysed at 6 months.
How precise (for example, in terms of confidence interval and	Precise	The p-values suggest high probability of significance ($p < 0.0001$) for all statistical comparisons reported (including proportion of therapy responders and reduction in number of

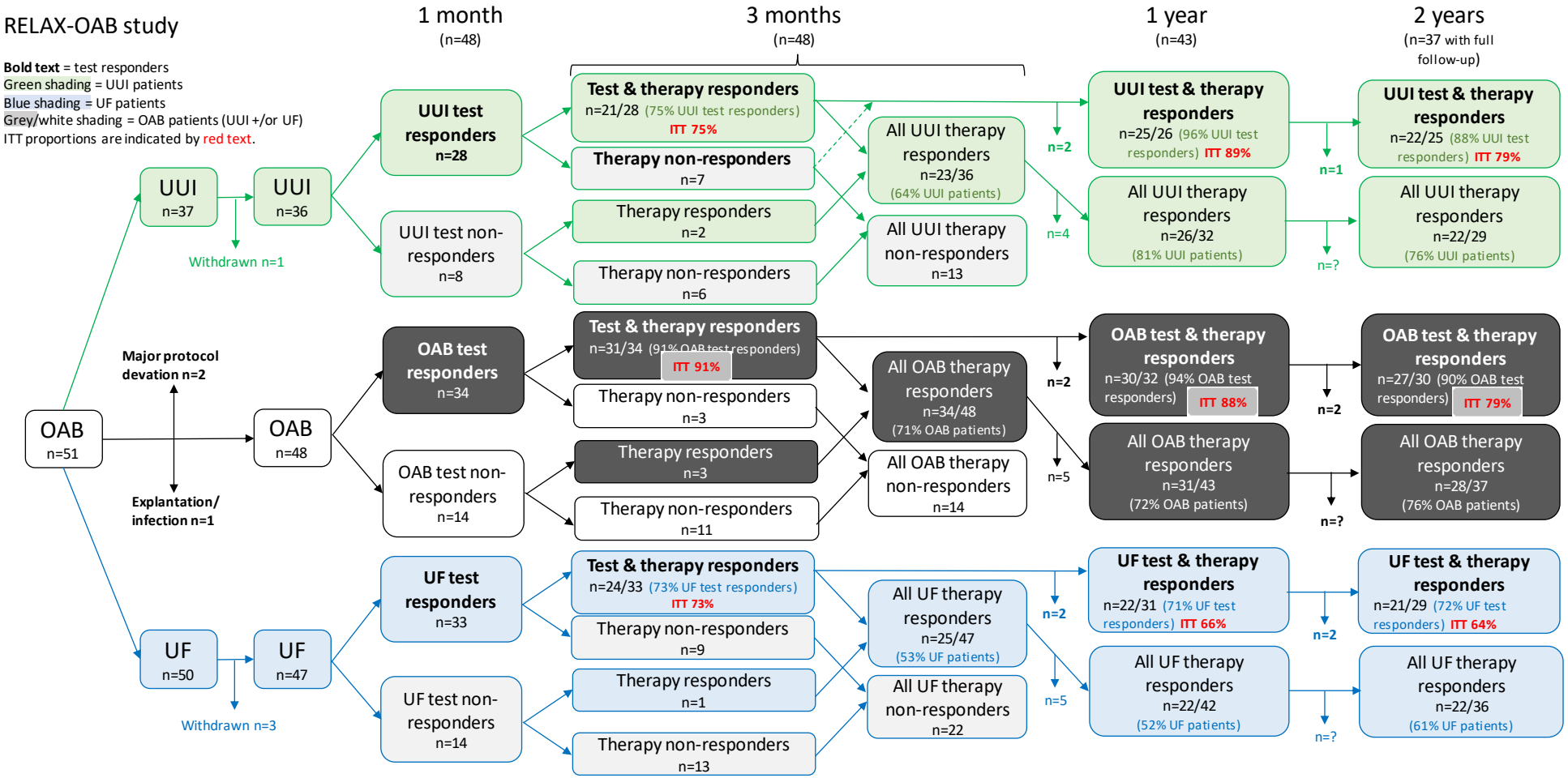
p values) are the results?		UUI episodes). Although confidence intervals are not reported, standard error values suggest low variation in key outcome measures.

Study name: RELAX-OAB, Blok (2018, 2019a); Unpublished: Blok (2019b)		
Study question	**Response**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Not clear	Prospective 'before and after' study with informed consent. Not clear whether recruitment was consecutive. Strict exclusion criteria could have introduced selection bias. Study was funded by the company. No sample size calculation was reported.
Was the exposure accurately measured to minimise bias?	Yes	All eligible patients received the same implant. A single-stage procedure was used, unlike standard care where an external test is first carried out.
Was the outcome accurately measured to minimise bias?	Not clear	**At 3 months**, the primary hypothesis was stated as "the mean change in ICIQ-OABqol score between baseline and 3 months is > 0". It is not clear whether this subjective outcome measure was pre-specified. The MCID for this measure is 10 points. The 'patient satisfaction questionnaire' is not referenced, and may not have been adequately validated. Likert scale options appear ambiguous (Blok 2019a, figures 5 and 6), although better granularity can be found in Blok et al. (2018). The method of administration of the patient satisfaction questionnaire is not reported, and may have influenced the subjective responses.
Have the authors identified all important confounding factors?	Not clear	One of the exclusion criteria is particularly broad/vague: "Any significant medical condition that is likely to interfere with study procedures, device operation, or likely to confound evaluation of study endpoints". Patients with neurological conditions were also excluded.
Have the authors taken account of the confounding factors in the design and/or analysis?	Not clear	Individuals with comorbidities considered likely to confound results were not eligible for participation. By excluding these people from the outset, the results may not be representative of the UK NHS patient population.
Was the follow-up of patients complete?	Yes	**At 1 year,** 8 people had been excluded from analyses: 2 for major protocol deviations (incomplete baseline diaries); 3 lost to follow-up or voluntarily withdrawn; and 3 explanted (1 procedure related infection and 2 lack of efficacy). **At 2 years** [unpublished data], data were incomplete for n = 14 in total: 2 incomplete baseline diaries; 4 lost to follow-up or voluntarily withdrawn; 7 explanted; 1 incomplete 2-year diary. Reasons for explantation: • 1 procedure-related infection • 4 due to lack of efficacy

		• 1 due to high impedances • 1 due to the need for an MRI scan (prior to its approval for use with full-body scans) All 14 were excluded from (per protocol) analyses in the publications at 2 years, but were not excluded from (ITT) analyses in the company submission.
How precise (for example, in terms of confidence interval and p values) are the results?	Precise	Confidence intervals are not reported; standard error values suggest low variation in key outcome measures. Where p-values are reported, all are $p < 0.001$. Caution is advised in the absence of a sample size calculation and ambiguity about the associated primary outcome measure.

12.3 Appendix C – Flow diagram with details of subgroup calculations (RELAX-OAB study)

Note: Some of the numerators were retrospectively calculated/estimated based on available information. 2 year data were obtained from unpublished materials.



12.4 Appendix D - Quality appraisal of economic evidence

Noblett *et al.* (2017) (based on the checklist from NICE manual Appendix H page 9; original source: Philips *et al.* (2004)) and the differences between Noblett *et al.* (2017) model and the company's submitted model.

Section 1: Applicability	**Yes/partly/ no/unclear /NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	The methodology states: 'population was assumed to resemble OAB patients with characteristics similar to those implanted with SNM, based on the most recently reported data of the InSite OAB study'. Study was performed in US
1.2 Are the interventions appropriate for the review question?	Yes	
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	No	Based on US system, but the model EAC received is adapted to UK system
1.4 Is the perspective for costs appropriate for the review question?	Partly	Takes into account healthcare system, but not personal social services (PSS) perspective
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Unclear	The paper mentions that all costs were discounted with rate of 3% per year but actual calculations are not available
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	N/A	Not use QALYs
1.8 **Overall judgement: Directly applicable**~~/partially applicable/not applicable~~ There is no need to use section 2 of the checklist if the study is considered 'not applicable'.		
Other comments:		
Section 2: Study limitations (the level of methodological quality)	**Yes/partly/ no/unclear /NA**	**Comments**
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	All relevant health states are included
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	
2.3 Are all important and relevant outcomes included?	Yes	Model assumes that the clinical outcomes are the same; only investigates the impact of battery lifetime on costs

2.4 Are the estimates of baseline outcomes from the best available source?	No	The Table I lists referenced used for each parameter, however, the relevant information were not found in the papers or the reference does not exist on the reference list. Lots of assumptions based on information from clinical experts. The study conducted by the same main author as the InSite study was used as a source of clinical and safety data. References include only observational studies.
2.5 Are the estimates of relative intervention effects from the best available source?	Unclear	Intervention effects are assumed the same for both devices
2.6 Are all important and relevant costs included?	No	There is no information about staff training and costs associated with that
2.7 Are the estimates of resource use from the best available source?	Partly	As above. Cost of treatment of adverse events (e.g. antibiotics) are incorporated, but without details
2.8 Are the unit costs of resources from the best available source?	Unclear	Unclear what antibiotics are used; how frequently and in what dose
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	NA	ICER not calculated
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	No	Sensitivity analysis didn't cover infection rates and their impact on costs
2.11 Has no potential financial conflict of interest been declared?	No	The study, and study authors, were supported by the manufacturer of a rechargeable SNM device (Axonics)
2.12 **Overall assessment:** ~~Minor limitations/~~**potentially serious limitations**~~/very serious limitations~~		
Other comments: • Not sure how discontinuation rates were calculated (if added up or calculated based on the cohort alive) • Testing before the implantation is not taken into account during cost evaluation • Some study parameters on clinical and safety of the devices (parameters not stated) were derived from the study carried out by the same main author (funded by the manufacturer of the non-rechargeable device) • The time point used in sensitivity analysis (compliance of patients) differs between methodology and results.		

Differences	Noblett *et al.* (2017)	Submitted model	Comments
Device	Rechargeable spinal cord stimulation systems (Eon Mini Rechargeable IPG, Nevro Senza SCS system)	Rechargeable sacral neuromodulation system (Axonics)	Potentially different clinical effectiveness and/or device costs
Battery lifetime	10 years	15 years	Longer device lifetime in the submitted model
Budget Impact Analysis	Total SNM population/ per patient analysis	Per cohort of 25 patients	
Adverse events (Lead migration/dislodgement; lead fracture)	Rates applied at index and subsequent replacement procedures	Rates applied only at index procedure	Not applying rates to subsequent procedures will affect overall costs
Discount rate	3%	3.5%	Differences between countries; not much impact on costs (both scenarios will be discounted at the same rate)
Payment systems	Mix of Medicare and private payers	NHS patients only	Differences in costs and reimbursement system
Mortality rates	Based on US life tables	Based on UK life tables	Appropriate for the model
Therapy discontinuation	Not clear how calculated for each progression in the model	Cumulative discontinuation calculated by adding all rates	Cumulative discontinuation should be corrected in the model
Sensitivity analysis (patients compliance with recharging requirements)	Assumption that 20% of patients with rechargeable device will get a non-rechargeable device after 4/4.5 years (time not consistent between methods and results)	Not performed	
Sensitivity analysis (lead replacement)	Lead replacement every 5 years despite longer neurostimulator lifetime	Not performed	
% of rechargeable device in the first year	20%	30%	Sources of information not stated
% of increase in use of rechargeable device per year	20%	10%	Sources of information not stated

12.5 Appendix E - Stress test performed on the model submitted by the company.

Scenario	Axonics	Comparator	Difference	Comment
Base case	£21,223	£27,261	-£6,038	
Set Axonics cost to zero *Detailed inputs 4 D10*	£11,047	£27,261	-16,214	As expected, comparator cost stayed the same, Axonics becomes very cheap
Set comparator cost to zero *Detailed inputs 4 D9*	£21,223	£19,297	£1,926	As expected, comparator becomes cheaper
Set number of patients implanted per year to 0 *FRONT END – UK D7*	#DIV/0!	#DIV/0!	#DIV/0!	As expected
Set number of patients implanted per year to 250 (x10) *FRONT END – UK D7*	£21,233	£27,261	-£6,038	As expected, cost per patient does not change
Set required stimulator replacement (battery), Rechargeable (yrs) to 4.4 *Detailed inputs 1 D35*	£32,765	£27,261	£5,504	As expected, cost of Axonics increased due to a high equipment cost at the same replacement rate.
Set required stimulator replacement (battery), Rechargeable (yrs) to 7.5 (half expected life) *Detailed inputs 1 D35*	£26,605	£27,261	-£656	Axonics device still more cost effective if battery life half of expected life.
Set required stimulator replacement (battery), Rechargeable (yrs) to 15 *Detailed inputs 1 D34*	£21,223	£17,397	£3,826	As expected, comparator becomes cheaper. Cost of equipment is cheaper and doesn't include a charger.
Set Rechargeable SNS discontinued (3 month prob., 1st year) to 100% *Detailed inputs 1 D14*	£32,278	£27,261	£5,017	These results are due to the incorrect calculation of the cumulative discontinuation rate. The effect is that there are large negative numbers of patients with the implant, and replacement results in a
Set non-rechargeable SNS discontinued (3 month prob., 1st year) to 100% *Detailed inputs 1 D10*	£21,223	£3,214	£18,009	

				negative cost. Thus in this situation the treatment gets cheaper over time. This is obviously a modelling artefact, not a possible real situation. There is less impact on the Axonics arm, as there is only one replacement procedure. As there are more patients with the implant, over time, then the cost of adverse events also increases. With the EAC corrections, the impact is greatly reduced
Set device cost – Axonics (rechargeable) to 0 *Detailed inputs 4 D14*	£17,907	£27,261	-£9,353	As expected
Set device cost – InterStim (non-rechargeable) to 0 *Detailed inputs 4 D13*	£21,223	£15,815	£5,408	As expected
Set Device Replacement Needed to 100% *Detailed Inputs 3 D6*	£21,686	£27,878	-£6,191	Cost increased, but would have expected a larger increase
Set Lead migration/dislodgement (rechargeable) to 100% *Detailed Inputs 1 D28*	£25,253	£27,261	-£2,008	Increases the cost of Axonics but interesting that it is still cheaper than comparator
Set Lead fracture (rechargeable) to 100% *Detailed Inputs 1 D31*	£25,238	£27,261	-£2,023	Increases the cost of Axonics but interesting that it is still cheaper than comparator
Double time horizon	£23,433	£34,143	-£10,710	As expected. Cost per patient decreases over time as Axonics requires replacement less frequently than comparator, whose costs

				increase due to the increased number of replacements.
Reduce time horizon to 3 months	£14,731	£12,431	£2,300	As expected as comparator is cheaper to implant and have not crossed a replacement threshold.
Set Medtronic IPG, TL and TL introducer kit to 0 (device cost) *Detailed inputs 4 H114*	£21,223	£9,555	£11,668	As expected
Set Axonics IPG to zero (device cost) *Detailed inputs 4 G114*	£10, 533	£27,261	-£16,727	As expected
Set female to 100%	£21,286	£27,341	-£6,055	Slightly higher costs for both arms due to longer life expectancy. Very small difference.
Set CPI Index to 1	£21,206	£27,241	-£6,034	Very small difference, most costs not inflated
Set cost of care for patients off therapy to zero	£20,759	£26,797	-£6,038	Slight reduction in cost, no impact on cost difference

12.6 Appendix F – Additional costing results

The following table gives additional information on how the company grouped different costs into the results table.

Device costs	Device costs from 'Whole system implant'
	Cost of charger (rechargeable device only)
	Initial/replacement of patient remote
	Device costs from 'Generator implant or replacement'
Administration costs	GP appointments from 'Cost of incontinence mgmt'
	Follow-up visits costs
	Removal
	Programming
	Procedure cost from 'Whole system implant'
	Procedure cost from 'Generator implant or replacement'
Consumables	Cost of pads from 'Cost of incontinence mgmt'
Adverse events – treatment costs	Cost of antibiotics and procedure from 'Treatment of surgical site infection'
	Revision and explanation procedure costs from 'Treatment of surgical site pain'
	Revision procedure costs from 'Lead revision'
	Procedure cost from 'Lead migration'
Adverse events – device costs	Device costs from 'Treatment of surgical site infection'
	Device costs from 'Treatment of surgical site pain'
	Device costs from 'Lead revision'
	Device costs from 'Lead migration'

The subsequent tables show the results for the EAC base case amended to use data from either the InterStim studies in both arms, or the Axonics studies in both arms. The tables also include results for the scenario with testing prior to full implant. Additional information about this scenario is in Appendix G.

	Axonics data only			InterStim data only		
	Technology	**Comparator**	**Cost saving per patient**	**Technology**	**Comparator**	**Cost saving per patient**
	Without testing			**Without testing**		
Device cost (without AE-related device costs)	13,289	18,266	-4,977	13,332	18,400	-5,068
Training costs	0	0	0	0	0	0
Administration cost	4,357	5,193	-836	4,324	5,172	-848
Monitoring costs	0	0	0	0	0	0
Consumables (incontinence pads for patients off SNM)	990	990	0	942	942	0
Adverse events (treatment and device costs)	1,177 (403 + 774)	1,020 (428 + 592)	157	1,666 (557 + 1,109)	1,566 (643 + 923)	100
Total	**19,812**	**25,469**	**-5,657**	**20,264**	**26,080**	**-5,816**
	With testing			**With testing**		
Testing costs	3,503	3,099	404	3,503	3,099	404
Device cost (without AE-related device costs)	6,553	10,376	-3,823	6,581	10,464	-3,883
Training costs	0	0	0	0	0	0
Administration cost	4,545	3,992	553	3,971	4,531	-560
Monitoring costs	0	0	0	0	0	0
Consumables (incontinence pads for patients off SNM)	2,224	2,224	0	2,192	2,192	0
Adverse events (treatment and device costs)	778 (266 + 512)	674 (283 + 391)	104	1,102 (369 + 733)	1,035 (425 + 610)	67
Total	**17,049**	**20,917**	**-3,868**	**17,348**	**21,322**	**-3,974**

12.7 Appendix G - Testing prior to implant

UK clinical pathways

In the UK, patients who are candidates for sacral nerve stimulation will initially have an evaluation period. This is used to help both the patient and clinician decide if SNM will be beneficial, assess the nerve integrity and identify the optimal lead location. There are two techniques used in the UK: Percutaneous Nerve Evaluation or Staged implantation.

Percutaneous Nerve Evaluation involves the temporary placement of a lead without a retention mechanism connected to an external stimulator. It is typically performed under local anaesthesia. If the test is successful the temporary lead is removed and replaced by tined leads connected to an implantable pulse generator. PNE is limited by lead migration which is common in active or obese patients.

Staged implantation involves a fluoroscopically guided placement of a permanent tined lead. The tined lead decreases the rate of lead migration. In stage 1 implantation, the lead is connected to an external stimulator. If the test is successful the patient will move to stage 2 implantation. An implantable pulse generator replaces the external stimulator, using the original tined leads.

Submitted model with testing scenario

In the submitted model the base case does not include any testing, as it is assumed to have the same costs and outcomes for each arm. The model includes an optional scenario with three testing states, percutaneous nerve evaluation, staged tined lead or unstaged (no testing). As a proportion of patients goes down each pathway, there are a number of resources associated with testing.

For the decision tree, the probabilities of using testing strategies and their success is based on assumptions and publication by Leong *et al.* (2010).

Results from testing scenario

The cost saving from the testing scenario is reduced, as only the test responders receive the cost saving intervention. The non-responders in both arms receive conservative care (continence pads and GP visits), and costs are the same for both arms.

	Company's results			EAC results		
	Technology	Comparator	Cost saving per patient	Technology	Comparator	Cost saving per patient
With testing						
Testing costs	£3,587	£3,128	-£459	£3,503	£3,099	-£404
Device cost (without AE-related device costs)	£7,341	£11,020	£3,679	£6,553	£10,464	£3,911
Training costs	0	0	0	0	0	0
Administration cost	£4,304	£4,936	£632	£3,992	£4,531	£539
Monitoring costs	0	0	0	0	0	0
Consumables (incontinence pads for patients off SNM)	£1,870	£1,870	0	£2,224	£2,192	-£32
Adverse events (treatment and device costs)	£606 (222 + 384)	£650 (300 + 350)	£44	£778 (267 + 511)	£1,039 (427 + 612)	£261
Total	**£17,708**	**£21,604**	**£3,896**	**£17,049**	**£21,325**	**£4,275**

NICE Medical technologies guidance

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

External assessment centre technical assessment report

Work package ref	RX238
Work package name	Axonics technical assessment
Produced by	Newcastle EAC
Main Authors	Katrin A. Bangel, Helen Cole, Michael Drinnan
Correspondence to	Helen Cole …. Email: [redacted]
Date completed	17th January, 2020

Declared interests of the authors: None

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

CONTENTS

Introduction and scope

NICE is currently developing Medical Technologies Guidance on the Axonics sacral neuromodulation (SNM) system for bladder control in people with symptoms of overactive bladder. NICE has previously published a Medtech Innovation Briefing on the system for overactive bladder and faecal incontinence (MIB164, December 2018).

SNM therapy is delivered by a stimulator implanted subcutaneously in the upper buttock. The stimulator generates electric pulses; lead electrodes implanted through the corresponding sacral foramen transmit these pulses from the stimulator to the sacral nerves.

The stimulator is powered by a rechargeable battery; presently this device is the only rechargeable SNM system on the market. Axonics claim therapeutic equivalence to existing SNM devices that have a primary (non-rechargeable) battery. The unique claim of Axonics' SNM is to reduce the number of invasive stimulator replacement procedures needed, which would typically be required every 3 to 5 years with a non-rechargeable system: "*The Axonics battery embedded in the Neurostimulator is qualified by robust testing to function for at least 15 years, obviating the need for recurring surgical explant and replacement. This not only reduces exposure to adverse events associated with repeat surgeries for patients, but also generates a significant cost saving opportunity to the National Health System.*" (Company evidence submission (part 1) for MT417 Axonics SNM System for OAB; Page 10).

Battery life is a key consideration in the cost consequence analysis (CCA) of the Axonics SNM stimulator. This stimulator's battery has a claimed life of at least 15 years, longer than comparator non-rechargeable SNM devices. However, a crucial limitation of existing evidence in the main assessment report is a lack of long-term outcome data. Accelerated testing of the rechargeable battery has been carried out by Axonics in order to support the claimed 15-year life of the battery.

Clearly, making use of long battery life requires that the stimulator not be removed for other reasons. Therefore in addition, data on the technical issues of lead migration and MRI compatibility were requested from Axonics.

Newcastle External Assessment Centre (EAC) was commissioned by NICE to evaluate these additional technical data in order to support the Medical Technologies Advisory Committee (MTAC)'s production of draft guidance on Axonics. In this report, which is supplementary to the main assessment report, we provide advice on the technical areas identified by the NICE technical team. In particular the following questions are addressed:

How does the technical evidence on Axonics SNM technology support the claims made by the company with a focus on battery life span and MRI compatibility of the device?

What factors affect the longevity of the rechargeable battery? Were these included in the testing?

Does the technical evidence demonstrate technical equivalence with other SNM systems currently available in the NHS?

This question was discussed with the NICE technical team before commencing the technical assessment. It was agreed that this question would be limited to claims on battery life and MRI compatibility only and would be answered by Newcastle EAC using public information on comparator technologies. Other companies were not asked to submit technical evidence for this assessment.

Does the technical evidence address the related issue of lead migration?

As well as answering the specific questions, the technical assessment includes a description of the available technical evidence on:

The life span of the rechargeable battery, including an evaluation of the quality and quantity of the evidence and a summary and conclusions of the results.

A description of the gold standard of technical evidence in this area, in relation to that available for Axonics.

Any relevant standards e.g. IEEE.

Again, this was clarified with the NICE technical team that Newcastle EAC was to identify any standards relevant to medical device battery life expectancy and MRI compatibility in adequate detail to inform whether there are relevant standards (or not). For MRI, a confirmation of acceptable Tesla thresholds for the device would be useful.

We present our report in four parts:

First, we assess the technical evidence for the life span of the rechargeable battery.

Second, we report on the technical evidence for lead migration.

Next, we report on the MRI compatibility status of Axonics SNM.

Finally, we provide a summary answer to each of the four technical questions in this assessment.

Axonics technical evidence submission

Axonics provided NICE with the following summary documents and suite of confidential test reports on 04/12/2019, containing evidence in support of the usable battery life of their SNM stimulator and MRI compatibility:

Document name / reference	Confidentiality status
Axonics Life Test Summary.docx	Disclose permitted
Testing on MRI compatibility.docx	Disclose permitted
Test reports to demonstrate 15 years longevity	
0037_RevB_Test_Protocol,_IPG_Battery,_Accelerated_Life_Testing.pdf 106-0037_RevB_Test_Protocol,_IPG_Battery,_Accelerated_Life_Testing.pdf 106-0037-002rA_Test_Report_IPG_Battery_Accelerated_Life_Testing_for_750_Cycles.pdf 106-0037-002rA Attachment 1 - Equipment Datasheet 106-0037-002rA Attachment 2 - SN0002187 Datasheets 106-0037-002rA Attachment 3 - SN0002188 Datasheets 106-0037-002rA Attachment 4 - SN0002190 Datasheets 106-0037-002rA Attachment 5 - SN0002191 Datasheets 106-0037-002rA Attachment 6 - SN0002192 Datasheets 106-0037-002rA Attachment 7 - SN0002193 Datasheets 106-0037-002rA Attachment 8 - SN0002194 Datasheets 106-0037-002rA Attachment 9 - SN0002195 Datasheets 106-0037-002rA Attachment 10 - SN0002196 Datasheets 106-0037-002rA Attachment 11 - SN0002197 Datasheets 106-0037-002rA Attachment 12 - SN0002198 Datasheets 106-0037-002rA Attachment 13 - SN0002199 Datasheets 106-0037-002rA Attachment 14 - SN0002200 Datasheets 106-0037-002rA Attachment 15 - SN0002201 Datasheets	All confidential data
110-0010-001rM_Charging_System_Manual_English_(CONTENT_ONLY).pdf 110-0003rM_Neurostimulator_Implant_Manual_(SCD)_–_1101.pdf 110-0044-001rD_Remote_Control_Manual,_English,_US_(CONTENT_ONLY).pdf 110-0059rD_Tined_Lead_Kit_Manual_(SCD).pdf	Disclose permitted
Test reports to demonstrate MRI compatibility	
104-0082-001rC_Test_Report_MRI_Conditional_Labeling.pdf 104-0082rG_Test_Plan,_MRI_Conditional_Labeling.pdf	All confidential data
110-0003rN_Neurostimulator_Implant_Manual_(SCD).pdf	Disclose permitted

110-0069-001rH MRI Full Body Guidelines for the Axonics SNM Therapy.pdf 110-0074-001rF MRI Patient Guidelines for the Axonics SNM System.pdf	
Test reports on ceramic ageing, not used	
106-0006-001rA Attachment A - Test Datasheet 106-0006-001rA Attachment B - Sample Observations 106-0006-001rA Test Report, Ceramic Aging 106-0006-002rA Attachment A, Test Data Sheet and Sample Observations 106-0006-002rA Test Report, Ceramic Aging, Vacuum 5 106-0006-003rA Attachment A, Test Data Sheet and Sample Observations 106-0006-003rA Test Report, Ceramic Aging, Vacuum 6 106-0006rC Test_Protocol,_Ceramic_Aging 106-0103-001rA Attachment 1- Test Datasheet 106-0103-001rA_Test_Report_Bend Fatigue Testing_90 Degree, Permanent Lead 106-0126-001rA Attachment 1- Test Datasheet 106-0126-001rA_Test_Report_Bend Fatigue Testing_45 Degree, Permanent Lead 106-0127-001rA Attachment 1- Test Datasheet 106-0127-001rA_Test_Report_Bend Fatigue Testing_22.5 Degree, Permanent Lead 106-0128-001rA Attachment 1- Test Datasheet 106-0128-001rA_Test_Report_Bend Fatigue Testing_5 Degree, Permanent Lead	All confidential data

Technical evidence on battery life

Axonics provided two summary documents and three confidential test reports containing evidence used to evaluate of the usable battery life of their SNM stimulator.

Evidence

[redacted]

Assumptions

- Mean stimulator lead impedance of 1400 ohms
- Typical recharge interval of 2 weeks.
- Nominal stimulation parameters of 2mA, 210µs pulse width and 14Hz repetition rate. (Axonics Life Test Summary.docx, disclose permitted)

Claims

The claims for battery life in terms of recharge cycles are given in the table, taken from Axonics' submission of 'Axonics Life Test Summary.docx' (disclose permitted):

Description	Amplitude (mA)	Rate (Hz)	Pulse width (µs)	Mode	Electrodes	Recharge Interval (days)	# of recharge cycles in 15 years
High energy	2.9 mA	14	210	Continuous	Bipolar, 2 active	10	550
Moderate energy	2.1 mA	14	210	Cycling: 16s ON, 8s OFF	Bipolar, 2 active	15	375
Low energy	1.4 mA	10	210	Cycling: 16s ON, 8s OFF	Bipolar, 2 active	24	230

Table 1. Outcomes of Axonics stimulation battery accelerated life testing, adapted from 'Axonics Life Test summary'(disclose permitted).

In summary of this table, Axonics write that: "*even in the worst case, the battery will undergo at most, 550 charge and discharge cycles in a 15 year period. Axonics tested the battery to last 1,000 charge discharge cycles with minimal capacity loss. Therefore, it is reasonable to claim a 15 year usable life"*

And: "*Our clinical experience indicates that the typical recharge interval is 2 weeks for patients who have the nominal stimulation parameters (2mA, 14Hz and 210µs). At this charge interval, 390 cycles is equivalent to 15 years of clinical use.*" (Axonics Life Test summary, disclose permitted).

Technical details of stimulator battery

[redacted]

Assessment of battery test protocol

Standards and best practice for lithium batteries

We note that the relevant European standard (EN 61960 7.6.3) defines a method for measuring battery endurance (*Section 7.6.3: Endurance in cycles at a rate of 0,5 I_t accelerated test procedure*).

The standards determine the number of charge/discharge cycles which a cell or battery can endure before its useful capacity has been significantly depleted or the remaining capacity after a specified number of cycles (see also **Figure 2**)

"Prior to charging, the cell or battery shall be discharged at 20 °C ± 5 °C at a constant current of 0,5 It A, down to a specified end-of-discharge voltage. An endurance test shall then be carried out, irrespective of cell designation, in an ambient temperature of 20 °C ± 5 °C. The remaining capacity obtained when the test is completed shall be not less than 60 % C5 Ah." (International Electrotechnical Commission, 2012).

[redacted]

Cycle number [a]	Charge	Stand in charged condition	Discharge
A: 1-400 or B: 1-300	Method declared by the manufacturer	0-1 h	0,5 I_t A to final voltage

[a] A: for cells, B: for batteries.

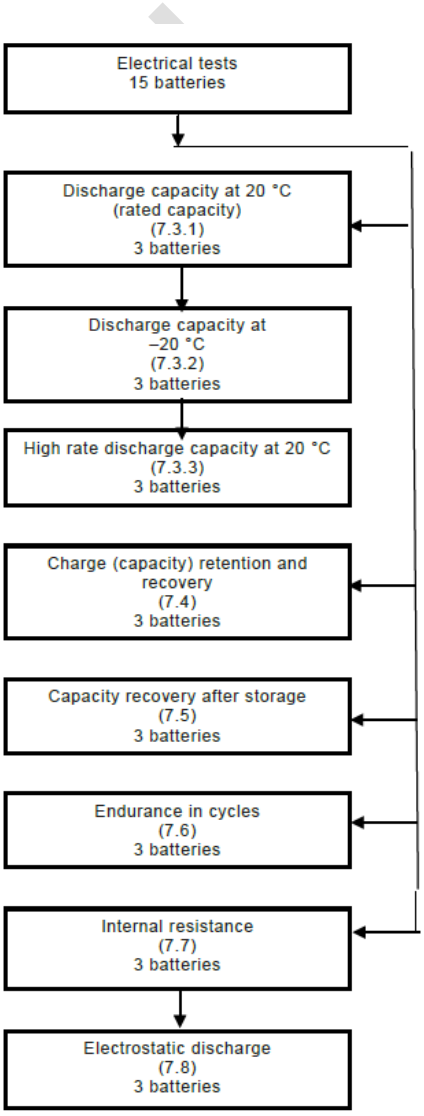


Figure 2. Sequence of tests (upper part) and endurance in discharge cycles at a rate of 0,5 *I*t A (lower part) according to EN 61960 standard (International Electrotechnical Commission, 2012).

Discharge test calculations

[redacted]

Test cycling

"We further tested the implantable batteries to 1,000 charge-discharge testing cycles. The batteries still retained more than 88% of their initial battery capacity after 1,000 cycles, equivalent to 38 years of lifetime. This test data strongly support that Axonics implant battery can last at least 15 years inside a human body without seeing significant performance degradation."

"The Axonics Neurostimulator battery has been tested through a total of 1,000 charge/discharge cycles with less than 20% loss in performance. For an average charging interval of 2 weeks (charging every 2 weeks), this corresponds to 40 years of life. For an average charging interval of 1 week (charging every week), this corresponds to almost 20 years of life (1,000 cycles / 52 weeks = 19.2 years)."

[redacted]

Missing evidence

[redacted]

Non-sequential battery numbering

[redacted]

Test results

[redacted]

Assessment of battery life assumptions

Battery life model

[redacted]

Evidence for the battery life mathematical model

Predicted charging intervals are given in table 1 (*above*) and in **table 3** (Blok et al., 2019). These predictions must presumably be backed by a mathematical model that predicts battery discharge time in terms of stimulus parameters and battery capacity.

		Stimulation Settings (mean ± std)			
Visit	***n***	**Amplitude (mA)**	**F (Hz)**	**Pulse width (µs)**	**Impedance (Ohms)**
Post-implant	51	1.1 ± 0.8	14 ± 0	209.4 ± 4.2	1005 ± 292
2 weeks	51	1.5 ± 1.1	14 ± 0	209.4 ± 4.2	946 ± 187
1 months	50	1.6 ± 1.1	13.9 ± 0.6	208.8 ± 6	964 ± 161
3 months	48	1.7 ± 1.1	14.3 ± 1.6	210.6 ± 11.6	1201 ± 214

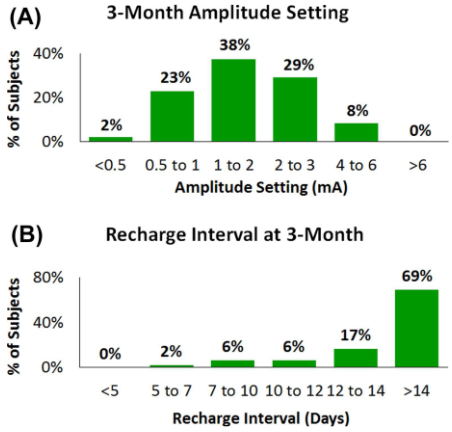


Table 3. Stimulation characteristics at follow-up visits from RELAX-OAB study (Blok et al, 2019)

There are several external and internal stress factors that affect battery aging and we consider these below:

Charging and the SmartCharge algorithm

It is well-recognised that lithium-ion batteries require careful management to maintain their performance. We note the proprietary *SmartCharge*™ algorithm for battery management which may affect battery capacity and has not been presented in evidence. For example, lithium ion battery management may limit the charge and discharge levels to help preserve battery life. In which case, the test figures for battery capacity may not reflect real-world performance. It is not clear how the battery capacity calculated in the test reports relates to the battery capacity as managed by the *SmartCharge*™ algorithm, since the algorithm is not disclosed.

Lead impedance

The cited nominal lead impedance of 1400 ohms is the mean value taken from a non-discussion poster presented to the American Urogynocological Society: (Noblett et al., 2014)

In the implant manual for the stimulator, the nominal lead impedance used as the basis of battery life estimation is given as 1600 ohms. In the RELAX-OAB study, lead impedance at 3 months is given as mean (SD) 1201 (214) ohms (Blok et al, 2019)

It appears that lead impedance has been used in the battery life model to estimate stimulation current at 12 months. Variable impedance or impedance that is different to the value used in the model may have an adverse effect on battery life; see later discussion of stimulation current.

Recharge interval

Table 1 suggests between 230 and 550 charge cycles per 15 years, depending on stimulus regime. From Axonics' submission: "*Typical recharge interval is 2 weeks with nominal stimulation parameters (2mA, 14Hz and 210μs) based on clinical experience. At this charge interval, 390 cycles is equivalent to 15 years of clinical use. The charge-discharge testing on our implant battery showed that, after 390 cycles later, the battery still retains 97% of the initial battery capacity."*

Or: "*From this table, we can see that even in the worst case, the battery will undergo at most, 550 charge and discharge cycles in a 15-year period.* (Axonics Life test summary, disclose permitted)

It is not clear if this recharge regime is device-led or patient-led. In our view this model does not seem reasonable, or indeed consistent with Axonics' advice to patients: *"Develop a habit for charging that fits your schedule, e.g. every Sunday while watching your favourite TV show. You do not need to wait for the stimulator battery to be low to charge."* (110-0010-001rM Charging System Manual, Axonics, 2019)

If a patient adopted this advice of charging once per week which appears likely, then they would require 780 recharge cycles per 15 years of use. If they adopted a more frequent charging regime, then correspondingly more cycles. Therefore a lifetime of 390 or 550 charge cycles seems inappropriately low; a 1-week nominal recharge interval would appear pragmatic. Nevertheless we note that evidence is provided for 750 recharge cycles.

We note that if the required recharge interval drops below the patient's preferred interval, this may lead to poor compliance. We imagine that for some patients, an inability to meet this 1-week charge cycle is considered as the endpoint to define battery failure (see the section of this report on: *Battery evaluations in Deep Brain Stimulation devices* and *defining end-of-life for a battery*).

Nominal stimulation parameters

Statistics in the submitted evidence are based on a typical stimulus current of 2.1 mA and a worst-case current of 2.9 mA, at 14Hz repetition frequency, 210 µs pulse width.

In the implant manual for the stimulator, the typical current is given as 1 mA and the worst-case used as the basis of battery life calculations is given as 4 mA stimulation current; these currents are delivered at 14Hz, 210 µs pulse width. No explanation is given for the discrepancy in the typical or maximum currents, i.e. why the typical and maximum currents presented in the evidence are different to those in the implant manual.

In the RELAX-OAB study, the workers report an impedance that may be as low as 1000 ohms; in series with a stimulation voltage of 4V this would imply a worst-case stimulation current of 4 mA, significantly higher than the 2.9 mA of the model.

At 3 months, mean stimulation current has risen from 1.1 to 1.7 (SD 1.1) mA. If we consider the mean + 2 SD as the upper limit of normal, this suggests a worst case in the region of 4 mA.

Finally, anecdotal evidence from clinical experts supports this worst-case: *The highest [stimulation current] I have ever had is 4.2mA* (personal communication from Chris Harding, consultant urologist).

Long-term effects on stimulation parameters

We note that long-term data are not available, but stimulation current was still increasing at 3 months. It is not clear why this is the case; it is possible the lead has migrated from its original site, or the patient has desensitised to the stimulus. It seems conceivable that the stimulation current would continue to rise somewhat over the 15 years of projected life.

The effect of long-term changes in electrode impedance is not clear. In a constant-voltage stimulator, an increased impedance would probably result in a reduced stimulation current from ohm's law ($I = {}^{V}/_{R}$ where V is constant, R is increasing). This would likely conserve battery life, but since physiological effects are typically related to current, the effectiveness of the stimulus would be reduced.

It seems plausible that Axonics' constant-current stimulus retains clinical effectiveness with changes in impedance, and adjustments to stimulus parameters are needed less frequently. However, increased impedance requires a higher stimulus voltage to deliver the same current (V=I.R where I is constant, R is increasing). The stimulus consumes more electrical power with an impact on battery life. Other stimulation parameters (frequency and pulse width) used in the battery life model appear consistent with the evidence from RELAX-OAB.

Patient preference data from deep brain stimulators

Deep brain stimulation (DBS) is increasingly used to treat a wide variety of neurological and psychiatric disorders. Like SNM stimulators, implantable pulse generators for DBS are available with non-rechargeable and rechargeable batteries. Clinical experts advised that, in general, these technologies

have published longer-term data than SNM stimulators, and highlighted a recently published patient preference survey, which may have generalisable findings to this assessment:

Khaleeq et al (2018) surveyed 30 consecutive adult patients with movement disorders attending a pre-DBS neurosurgery clinic at King's College Hospital, London, from August 2016 to April 2018:

- 19/30 patients (63%) with movement disorders chose the fixed-life battery & 11/30 patients (37%) chose the rechargeable battery.

- Most patients were not concerned about the size of the battery.

- 12/30 (40%) were concerned about surgery to replace the battery, and exactly the same number were concerned about the need to recharge the battery.

- 16/30 patients felt that an acceptable charging frequency was monthly or yearly.

- 12/30 felt a charging duration of 1 hour or more was acceptable, with 15/30 choosing less than 30 min.

- The main reasons cited for choosing the fixed-life battery were convenience & concern about forgetting to recharge the battery.

- The main reason for choosing the rechargeable battery was the avoidance of further surgery.

- Rechargeable batteries may be more acceptable if the recharging process is improved, more convenient, and discreet.

The authors plan a long-term follow-up patient satisfaction survey, to assess the post-implant opinions of this cohort on their choice of rechargeable or non-rechargeable device. Newcastle EAC therefore concludes that this study does not contain any generalisable data on patient compliance with increased frequency charging regimens as devices age. Any further literature review on patient preference was out with the scope of this technical assessment.

Defining end-of-life for a battery

[redacted]

Assessment of battery life mathematical model

[redacted]

Summary of battery life assessment

[redacted]

Technical evidence on lead migration & breakage

Evidence

[redacted]

Claims

[redacted]

Assessment of lead test evidence

Standards and best practice

EN 45502-2-2:2008 addresses implantable devices for tachyarrhythmia, which includes implantable defibrillators. Since there is no standard specifically for SNR devices, we believe this is a reasonable starting point. In the *Life Test Summary* document, ISO 14708-2:2012 is cited. It's not clear why there is a discrepancy between this and EN45502-2-2 cited in the formal submission at the top of the page.

Test protocol

[redacted]

Test results

[redacted]

Summary of lead test assessment

[redacted]

Technical evidence on MRI compatibility

Evidence

[redacted]

Claims

- Axonics SNS device is evaluated as "MR Conditional", meaning it demonstrated safety in the MR environment within defined conditions.
- Conditions are given in the Axonics literature; most importantly, the device should not be used in scanners beyond 3T field strength.

Limitations of MR safety testing

- The safety of the Axonics device has not been assessed in patients with other implanted devices in addition to the Axonics SNM System.

- MRI safety has NOT been evaluated under the following conditions: a broken lead, an intact tined lead without a neurostimulator, a partially implanted lead, a malfunctioning neurostimulator, or a neurostimulator with open or low impedances (indicating a short circuit) on any electrodes.
- Transverse Field MR systems have not been evaluated for scanning patients with the Axonics SNM System.
- External components of the Axonics SNM System (including the Clinician Programmer, Remote Control, Charger and Dock, and External Trial System (External Pulse Generator and percutaneous leads and cables) are unsafe to bring into the magnet room.
- No testing at magnetic fields above 3T has been done

MRI compatibility and associated risks for Axonics SNM

Some of the potential risks of performing MRI on a patient with an implanted Axonics SNM System include:

• Heating effects around the Axonics SNM System, especially the lead electrodes. If the specified MRI conditions are not observed, heating at a lead electrode can be higher than the established safety threshold. This may lead to burn injury or other damage to the sacral nerve and/or surrounding structures, which may be associated with pain and discomfort.

• Unintended stimulation due to current induced through the SNM lead wire. However, if the MRI scan is performed under the conditions specified in the manual, unintended stimulation to the surrounding tissue is unlikely. Risk of tissue damage due to current induced by the gradient or RF field is very low.

• Static magnetic field interactions including magnetic force and torque due to small amounts of material in the Neurostimulator being sensitive to magnetic fields. This may cause the Neurostimulator to shift or move slightly within the implant pocket and may place mechanical stress on tissues and the lead.

• Device malfunction or rectification can result in current induced through the SNM lead. The Axonics manual claims that *"Device malfunction or damage is unlikely if MRI scans are performed following the guidelines described in this document. If device malfunction or damage were to occur, it could cause discomfort, unintended stimulation, painful stimulation, or direct current stimulation, which may result in nerve damage and other associated problems. If a patient suspects a malfunction, he/she should be instructed to exit the magnet room and use the patient Remote Control or Clinician programmer to stop the stimulation. The patient should then contact their physician for further evaluation."* (Axonics, 2019). This information contradicts slightly the MRI guidelines which further state that all neurostimulation needs to be turned off during the MRI scan. Can unintended stimulation induced by the magnetic field can be stopped by the patient using the clinician programmer? Axonics might comment on this ambiguity, which could mislead physicians, MRI experts and/ or patients with potential consequences for patient safety.

• There is minimal image artifact when the device is out of the field of view. Image artifacts can result from the presence of the device within the field of view. Careful choice of MRI sequence parameters and location of the imaging plane may minimize MR image artifacts.

Source: 'Testing on MRI compatibility.docx' (disclose permitted)

Assessment of evidence on MRI compatibility

Standards and best practice

The most appropriate standard here is ISO/TS 10974:2018. According to this standard, potential health risks posed by MRI applied for SNS patients are heat, vibration, force, torque, unintended stimulation and device malfunction (see also **Table 4** & **Figure 2**)

General hazard	Test method	Clause
Heat	RF field-induced heating of the AIMD	8
	Gradient field-induced device heating	9
Vibration	Gradient field-induced vibration	10
Force	B_0-induced force	11
Torque	B_0-induced torque	12
Unintended stimulation	Gradient field-induced lead voltage (extrinsic electric potential)	13
	RF field-induced rectified lead voltage	15
Malfunction	B_0 field-induced device malfunction	14
	RF field-induced device malfunction	15
	Gradient field-induced device malfunction	16
	Combined fields test	17

Table 4 Potential patient hazards and corresponding test methods according to ISO TS 10974 (2018)

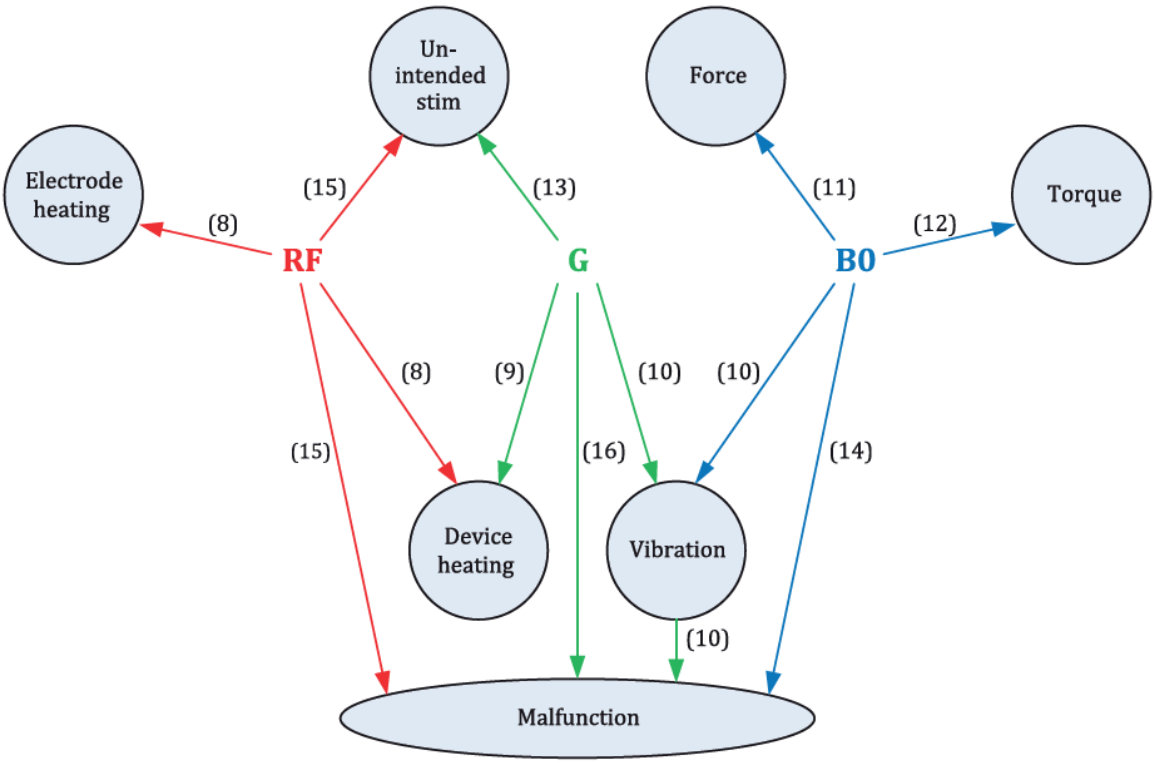


Figure 2 Relationship between MR scanner output fields (RF, gradient, *B*0) and hazards (test method clause numbers in parentheses) according to ISO standards

Test results

Test results: Heat

-RF-induced

[redacted]

-Gradient-field induced

[redacted]

Test results: Vibration

[redacted]

Test results: Force

[redacted]

Test results: Torque

[redacted]

Test results: Unintended Stimulation

[redacted]

Test results: Device Malfunction

[redacted]

Test results: Image artifacts

[redacted]

Specific Absorption Rate (**SAR**) which is a measure of the rate at which energy is absorbed by the human body when exposed to a radio frequency electromagnetic field, and others. For a full body scan

[redacted]

Summary of MRI compatibility assessment

- Axonics SNM is evaluated as "MR Conditional", meaning it demonstrated safety in the MR environment within defined scan parameters and other conditions.
- In the view of an MR expert: "*I think that scanning is likely to be feasible for many sequences as the device can be used in both 1.5T and 3T scanners and the SAR limits do not pose a huge barrier . . . eg. a simple scan that does not involve high duty cycle RF and amplitude / high*

switching rate gradients would be possible, but advanced sequences like some heavy-duty diffusion scans might be prohibited." [Personal communication from Pete Thelwall, Reader in MR Physics]

- Axonics' guidelines for professionals on their device's MRI compatibility (Axonics, 2019a, disclose permitted) are not completely clear whether the stimulator should be turned off and this needs clarification.
- Undetected broken leads or malfunctioning neurostimulators can pose a potential risk for MRI scanning and result in serious risks to the patient.
- Testing was done according to ISO/TS 10974:2012, test plan and test reports both claim to be reviewed to confirm compliance with ISO/TS 10974:2018. No such evidence is added though and all references to individual clauses in those reports are still made to the 2012 guidelines. This makes it challenging to verify compliance to new guidelines.

Summary of EAC findings

Considering battery life:

- The Axonics battery testing regime is not well-defined and contradicts itself in places.
- Battery life should be defined by the effect on the end user, rather than an arbitrary capacity in mA-hours. We suggest a better endpoint for battery failure would be a time-between-charges <1 week, particularly since Axonics recommend a weekly charging regime to their patients.
- With a typical or moderate stimulus of 2.1 mA that is maintained for the lifetime of the battery, it seems likely that the battery will exceed its claimed lifetime of 15 years.
- Based on evidence to date, we propose a worst-case stimulus current of 4 mA. Under these circumstances, we may expect a small proportion of devices to fail within their 15-year lifespan according to the '1 week' rule.
- There is little evidence available beyond 3 months of implant. However, the upwards trend in stimulus current gives some concern that end-of-life stimulus currents will exceed the 4 mA worst-case suggested from the 3-month data.
- These changes in stimulus current probably reflect the milder cases of lead migration, as well as other factors such as habituation to the stimulus.

Considering lead migration:

- The evidence for lead cycling appears compelling, and Newcastle EAC has no concerns that lead breakage due to fatigue is likely to present an undue problem.
- No specific technical evidence addressing lead migration was submitted by Axonics for technical assessment.
- In the case of minor lead migrations that can be compensated by increasing the SNM stimulus, we believe the battery life model will capture the effect, particularly as long-term data for lead impedance and stimulus current become available.
- In the case of major lead migrations and lead breakages, surgery is required to correct the adverse event. This is considered in the main assessment report.

Considering MRI compatibility:

- Axonics SNM device is evaluated as "MR Conditional", meaning it demonstrated safety in the MR environment within defined conditions.
- Conditions are given in the Axonics literature; most importantly, the device should not be used in scanners beyond 3T field strength.
- Axonics' guidelines for professionals on their device's MRI compatibility (Axonics,2019) are not 100% clear about that the stimulator should be turned off; we feel this needs clarification.
- Undetected broken leads or malfunctioning neurostimulators can pose a potential risk for MRI scanning and result in serious risks to the patient.
- Testing done according to ISO/TS 10974:2012, test plan and test reports both claim to be reviewed to confirm compliance with ISO/TS 10974:2018. No such evidence is added though and all references to individual clauses in those reports are still made to the 2012 guidelines. This makes it challenging to verify compliance to new guidelines.
- While case-by-case consideration is needed, it is likely that many MRI scans will be safe and effective.

Summary answers to the technical questions

1. How does the technical evidence on Axonics SNM technology support the claims made by the company with a focus on battery life span and MRI compatibility of the device?

Newcastle EAC response:

In terms of battery life:

The claims are partially supported based on the current evidence. If we consider typical stimulus parameters and use a recharge interval of <1 week as a definition of end-of-life, then we anticipate the lifetime of the battery to meet the manufacturers' claim of 15 years. If we consider the worst-case stimulus parameters with the same end-of-life criterion, then it is likely that some devices will fail prematurely. This assessment should be repeated with better long-term data on stimulus parameters.

In terms of MRI compatibility:

The company claims throughout their evidence submission that the Axonics SNM system is MRI "compatible". However, their Instructions for Use and associated MRI Guidelines clarify that the system was tested for compatibility with magnetic resonance imaging (MRI) using a head coil with 1.5 T and 3 T Systems and using a body coil with 1.5 T and 3 T Systems under certain additional conditions. The device is labelled as MR conditional, rather than MRI compatible and the scanning parameters are tabulated in (Axonics, 2019a, disclose permitted). - Nevertheless and while case-by-case consideration is needed, it is likely that many MRI scans will be safe and effective.

2. What factors affect the longevity of the rechargeable battery? Were these included in the testing?

Newcastle EAC response:

Lithium-ion battery life is affected by a complex set of factors, that include: temperature; charging regime; discharging profile; and other stress factors that are given in table 2. We note that the literature and manufacturer's datasheet describe a slow degradation in battery capacity in the region of 20% per 1000 cycles with long-term careful use.

Unless the battery fails catastrophically – not reported or assessed - the pragmatic endpoint comes when the recharge interval is too burdensome to fit with the patient's lifestyle. This will vary from patient-to-patient, but a nominal value of <1 week seems reasonable. Given the slow degradation in battery capacity, overwhelmingly the biggest factor is the stimulus parameters that have an enormous effect on the recharge interval. We have not had sight of the model used to estimate battery recharge interval, but our impression is of a pragmatic model using a worst-case battery capacity of 40 mA-h. In that sense yes, the important factors are included in the modelling. However, in our view the most clinically relevant endpoint is an inadequate recharge interval, rather than a reduced battery capacity.

3. Does the technical evidence demonstrate technical equivalence with other SNM systems currently available in the NHS?

Newcastle EAC response:

In terms of battery life: Yes. We anticipate that mean battery life will exceed that of Interstim, the main competitor technology. See also the response to point 1.

In terms of MRI compatibility:

Again, whilst Axonics incorrectly states that their system is fully compatible with MRI (for both head and body imaging), they also incorrectly state that the Medtronic InterStim comparator is not at all compatible: "*the Axonics rechargeable SNM device is fully MRI compatible up to 3 Tesla, while the non-rechargeable InterStim is not*." In fact, the Medtronic MRI Guidelines state that the InterStim system is labelled as MR Conditional for 1.5T head imaging, with conditional scanning parameters stated (Axonics, 2019a, disclose permitted).

Newcastle EAC concludes that the comparator is certainly more limited than the Axonics system, but both can be used under stated conditions for head MRI at 1.5T, whereas the Axonics has additional conditionality for head MRI at 3T and body MRI at both 1.5 and 3T. For both devices undetected damage of the stimulation device during MRI scanning can cause serious harm. Besides that, while Axonics claims to have based their testing according to the most up-to-date 2018 ISO standards, a closer look at the evidence suggests that their testing is mostly based on the 2012 standards.

In the absence of equivalent disclosure of technical data from Medtronic, we cannot determine whether the technical evidence demonstrates technical equivalence with the comparator.

Whether the additional conditions for MRI for Axonics (3T head scans and 1.5 T and 3 T body scans) compared with Medtronic InterStim (1.5 T head scans only) translate into significant benefits for very many patients in this cohort is outwith the scope of the technical assessment that Newcastle EAC is working on, but is in scope / outcomes of the main assessment.

Of relevance, the Medtronic InterStim Micro SNM system was submitted for FDA pre-market approval (PMA) in October 2019 and subject to approval will match the Axonics body MRI conditionality status (Medtronic, 2019).

4. Does the technical evidence address the related issue of lead migration?

Newcastle EAC response:

No, it does not. No evidence directly related to lead migration was submitted. Nevertheless, we have made some assessment as part of the overall picture of device or treatment failures. In particular, small lead migrations where the stimulator is still partially effective will impact battery life and are accounted for in the battery life model. Long-term data on stimulus parameters will be required to address the impact on device lifetime.

Complete lead failures are treated equivalently to a surgical intervention for any other adverse incident. These are within scope for the main assessment, and we have not considered these in this assessment report.

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Axonics (2019a).110-0069-001, Rev G, MRI Full-body Guidelines for the Axonics SNM Therapy System, English (Europe and Canada) (confidential)

Axonics (2019b), 106-0037-007rA, Test Report IPG Battery, Accelerated Life Testing for 750 cycles (confidential)

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

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

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It includes **brief** descriptions of the key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the company submission of evidence and with the EAC assessment report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

Key issues for consideration by the Committee are described in section 6, following the brief summaries of the clinical and cost evidence.

This report contains information that has been supplied in confidence and will be redacted before publication. This information is highlighted in blue. This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations
- Appendix D: Decision problem and claimed benefits

1 The technology

The Axonics rechargeable sacral neuromodulation (SNM) system is designed to have extended longevity compared to current non-rechargeable SNM devices. Axonics SNM delivers sacral nerve stimulation therapy through an implantable pulse generator (IPG) stimulator implanted subcutaneously in the upper buttock.

The stimulator generates electric pulses and is designed to allow adjustment of stimulation current according to tissue impedance. Lead electrodes implanted through corresponding sacral foramen transmit these pulses from the stimulator to the sacral nerves that control the bladder. The stimulator is powered by a rechargeable battery with an expected life span of at least 15 years, which is claimed to be longer than comparator non-rechargeable SNM devices. A handheld remote control activates the stimulator, adjusts the stimulation amplitude, and checks the battery status. A wireless charger, attachable to the skin over the implanted stimulator is used to charge the stimulator. It is claimed that the battery needs a recharge every 1-2 weeks for 30 minutes to 1 hour. The neurostimulator is smaller than comparator devices. Axonics SNM is compatible for full body MRI scans. Prior to 'permanent' implantation of the neurostimulator, responsiveness is tested using a test period of treatment using an external stimulator. Permanent implantation is usually done as a day case procedure and the device is programmed by a clinician.

The Axonics SNM system received a CE mark as a class III medical device in June 2016 for the treatment of symptoms of overactive bladder, faecal incontinence and urinary retention. This assessment focuses on symptoms of overactive bladder.

2 Proposed use of the technology

2.1 Disease or condition

Overactive bladder (OAB) is a condition that causes an urgent need to pass urine due to sudden contraction of the bladder. It may be caused by functional bladder disorders, but in most cases, the cause of OAB is unknown. Symptoms of OAB include impaired urine storage and bladder emptying resulting in urinary urge incontinence (a strong urge to urinate which is followed by an inability to stop passing urine) and symptoms of urgency-frequency (a need to pass urine more frequently than usual).

2.2 Patient group

The Axonics SNM system is intended for use in treating symptoms of OAB, specifically in people for whom conservative therapy and drug treatment have failed or are not suitable. The smaller size of Axonics SNM compared to other non-rechargeable SNM devices may make it beneficial to slim people with lower than average body mass index (BMI) and a lack of subcutaneous buttock fat. It is estimated that the prevalence of overactive bladder in adults aged 40 years and over in the UK is 19% (Milsom et al. 2002).

2.3 Current management

NICE's guidelines on urinary incontinence and pelvic organ prolapse in women and lower urinary tract symptoms in men recommend initial management of symptoms with conservative methods (such as lifestyle interventions, behavioural techniques and physical therapies) or drug treatment. When conservative methods and drug treatment fail, investigation to assess detrusor overactivity is recommended. If detrusor overactivity exists, botulinum toxin type A can be injected into the bladder wall. The use of botulinum injection may be associated with a need for clean intermittent catherisation or the use of temporary indwelling catheters. If a patient is unwilling to accept the possible risk of catherisation with botulinum injection or if botulinum injection fails, the NICE guideline on urinary incontinence and

pelvic organ prolapse in women recommends that percutaneous sacral nerve stimulation should be offered.

NICE's interventional procedures guidance on sacral nerve stimulation for urge incontinence and urgency-frequency suggests SNM as an option for people who have not responded to conservative management or drug treatment. Alternative invasive treatment options include irreversible bladder reconstruction (augmentation cytoplasty) and urinary diversion.

2.4 Proposed management with new technology

The pathway for the care of people with overactive bladder would not be changed by using the Axonics SNM system. The longer battery life could increase the time between replacements, thereby reducing the number of replacement procedures.

3 Company claimed benefits and the decision problem

Details of the decision problem and the company's claimed benefit are described in Appendix D.

The sponsor did not propose any variation to the decision problem. The EAC noted that although evidence from the two trials on Axonics SNM met the scope, the ARTISAN-SNM study had about a third of its population using medication alongside the Axonics device. This is not typical of refractory OAB in the UK but is reflective of a US population where refractory OAB is defined as having tried and failed at least two medications.

4 The evidence

4.1 Summary of evidence of clinical benefit

The company presented a total of 11 published articles (4 on Axonics and 7 on the non-rechargeable device Interstim) and 2 unpublished articles on the Axonics device. The EAC considered the company's search strategy for

clinical evidence, to be weak because only one database was searched, and the strategy lacked defined medical subject headings. The EAC ran a search across 10 databases and 2 clinical trial registries using a range of free text terms and subject headings, no further studies were identified. The EAC agreed that all 6 studies on the Axonics device were relevant to the scope. Studies that did not have Axonics SNM in the treatment or comparator arm were excluded. For further details see section 4 of company submission and section 3.1 of assessment report.

Table 1. Included studies, company and EAC

Study	Type of publication	Type of study	Comment
Studies included by both EAC and company			
6 studies McCrery (2019) Blok (2018a) Blok (2018b) Blok (2019a) Blok (2019c) Lane 2020 - ARTISAN SNM study	 Full paper Unpublished data Unpublished abstract	 Before and after study Before and after study Before and after study	
Studies in submission excluded by EAC			
Siegel 2015, Amundsen 2018 van Kerrebroeck (2007) Noblett (2016 and 2017) & Siegel (2016 and 2017)	Full paper Full paper Full paper	Randomised controlled trial Prospective study Prospective study	Axonics SNM not in treatment or comparator arm

The ARTISAN SNM (McCrery 2019 and Lane 2020) and the RELAX-OAB (Blok 2018a&b, Blok 2019a &c) studies were considered relevant to the scope. Both trials were before and after, intra-patient, observational studies reporting patient outcomes as a change from baseline. The existing studies are largely limited by a lack of long-term outcome data. Clinical effectiveness has not been demonstrated for longer than 2 years.

The EAC judged that there were similar design and reporting weaknesses across both trials. The company acknowledges limitations in published evidence arising from a lack of randomised trials and a lack of direct comparison between Axonics SNM and the standard care alternative (a non-rechargeable system). The EAC notes that lack of randomised recruitment may lead to bias in patient selection and surgical techniques and this could influence outcomes. RELAX-OAB and ARTISAN SNM studies differed in design due to a variation in the definition 'response to therapy' (see table 2 of the assessment report for definitions). Both studies had recruitment sites and authors in common, but recruitment periods did not coincide.

The RELAX-OAB study included 37 individuals with symptoms of urinary urge incontinence (UUI), and all except one (n=50/51) also had symptoms of urinary frequency (UF). Study authors report these results separately as well as combining them as a composite OAB score. Separation of subgroups is helpful, as clinical experts noted that treatment effectiveness is known to vary by indication. The ARTISAN-SNM study only includes individuals with UUI.

The EAC noted that study authors did not report consecutive recruitment of patients, the company however states there was consecutive recruitment, but did not describe how this was done. The EAC further highlighted that RELAX-OAB study excluded people with "any significant medical condition that is likely to interfere with study procedures, device operation, or likely to confound evaluation of study endpoints". During fact checking the company noted that this criterion was intended to exclude patients unable to operate the device and that no patient was excluded based on this criterion.

31% of patients in the ARTISAN SNM study were taking concomitant medication to treat the condition, the EAC noted the likelihood of an adjuvant effect, and this is inconsistent with the requirement that the population is refractory (McCrery 2019). The company states that this is reflective of a refractory OAB population in the US, who are defined as refractory based on having tried and failed at least 2 medications. Expert advice received by the EAC indicates that patients with a refractory OAB in the UK would not usually continue to take associated medications. Results of a patient survey (n=7) done by NICE's Public involvement programme (PIP) shows that some patients in the NHS had conservative therapy or drug treatment in addition to Axonics (Appendix C). During fact checking, the company stated that a post-hoc subgroup analysis conducted between subjects that took concomitant medications at baseline and subjects that did not take concomitant medications at baseline did not show a statistically significant difference in responder rates.

Patient histories varied as a result of prior treatments received. In ARTISAN-SNM, 13% (17/129) had received botulinum toxin therapy; 13% (17/129) had undergone tibial nerve stimulation; and 7% (9/129) had participated in a previous trial of an external SNM device. The RELAX-OAB study authors report that a total of 51% of participants had previously tried at least one other third line therapy for OAB. One quarter (25%) had received botulinum toxin therapy; 31% had undergone tibial nerve stimulation; and 20% had previous sling procedures (to treat stress urinary incontinence). Generalisability of the evidence may be limited because none of the studies was exclusively conducted in the UK and the proportion of patients from the UK study site is not reported.

The EAC noted that across both studies a significant improvement in quality of life was reported (see table 4 of assessment report). The EAC concluded that despite the limitations of the clinical evidence, the before and after improvements suggest that at least within the first 2 years, Axonics SNM can

significantly improve OAB and quality of life compared with a do-nothing scenario. This conclusion was supported by expert advice.

Table 1: Summary of pivotal studies (adapted from table 1 and table 3 of the assessment report)

Study and design	Participants/ population	Intervention	Outcome measures and follow up	Results	Withdrawals & adverse events	Comments
ARTISAN SNM study						
McCrery (2019)- 6 months follow up Before and after study	n = 129 with urinary urge incontinence n = 127 female; n = 2 male Average age (years): mean = 59.3, range = 21-86 *19 centres* US and Europe (The Netherlands, Belgium, France and UK)	*Participants implanted with tined lead and Axonics IPG in a single, non-staged procedure, without requiring prior testing with an external trial system*	All outcomes were compared to baseline. **Primary outcome measure:** Therapy responder rate (defined as ≥ 50% reduction in UUI episodes) at 6 months **Secondary outcomes:** Change in number of overactive bladder symptoms such as UUI episodes (leaks), urinary frequency (voids)	***Therapy responder rate*** **Of the initial UUI test responders (n=113), those who responded to therapy at:** **3 months:** 95% (n=107) ***6 months*** *95% (n=107; 95% CI 83, 95, p<0.0001) statistical significance refers to change from baseline* ***Symptom reduction 6months*** Mean (± SE) number of UUI episodes per day reduced from 5.6 (± 0.3) at baseline to 1.3 (± 0.2) at 6 months. **All participants**	**6 months** 3 people were withdrawn from the study within 6-months: 2 devices were explanted (1 postoperative wound infection; 1 because of pain unrelated to device). 1 person died (not device related). 10 device-related AEs (n = 10) at 6 months. 6 episodes (n = 6) of discomfort due to stimulation (resolved with reprogramming). 2 episodes (n = 2) of pain at the	The study design is a 'before and after' study therefore there is no separate comparator arm. Company funded study

			Change in Quality of life (ICIQ-OABqol score) ** Patient satisfaction** Ease and frequency of battery charging; acceptability of recharging experience.** Adverse events Number of explantations (with reasons)	79% reduction in number of UUI episodes per day for all participants. **Therapy responders** Of the therapy responders: 80% had a minimum of 75% reduction in number of UUI episodes per day at 6 months 34% were dry.	neurostimulator site (resolved spontaneously). 1 lead migration (successfully revised).	
Lane (2020), unpublished abstract – 12 months follow up Before and after study	As above	*As above*	As above at 12months	**Therapy responder rate *12 months*** **Of the initial UUI test responders (n=113), those who responded to therapy at:** **12 months:** 94% (n=106; 95% CI 83, 94, p<0.0001) **Symptom reduction** **12 months**	***12 months*** No serious device related incidents were reported. The total number of explantations at 12 months is reported by the company as 3% (of 129), but after excluding test non-responders this	

				Mean (± SE) number of UUI episodes per day reduced from 5.6 (± 0.3) at baseline to 1.4 (± 0.2) at 12 months ($p < 0.0001$). 77% responders had a minimum of 75% reduction in the number of UUI episodes per day; 29% were dry.	proportion is reduced to <1%. There was also 1 suspected lead fracture which required revision	
RELAX-OAB study						
Blok (2018a), 3 month results Blok (2018b), programming settings at 3 months. Blok (2019a), 12 month results Before and after study	n = 51 (n = 50 with urinary frequency, n = 37 with urinary incontinence) n = 38 female; n = 13 male Average age (years): mean = 51, range = 21-77 7 centres Europe (The	Participants implanted with tined lead and Axonics R-SNM in a single, non-staged procedure, without requiring prior testing with an external trial system.	All outcomes were compared to baseline. **Primary outcome measure:** Mean change in ICIQ-OABqol HRQoL total score at 3 months, compared to baseline.** **Secondary outcomes:** Responder rate (defined as ≥50% reduction	**Of the initial OAB test responders (n=34), those who responded to therapy at:** **3 months:** 91% (n = 31) **12 months:** 88% (n = 30) **Symptom reduction** **3 months:** In test responders, mean voids reduced by 6.6 per day. Incontinence episodes decreased by 6.3 ± 4.4 leaks per day. **12 months:**	No serious adverse device events were reported. 20 device-related AEs occurred in 13/51 people. 7/20 AEs occurred in the first 2 weeks. Undesirable or uncomfortable stimulation (13 events, n = 10), all resolved with reprogramming. Pain at the IPG implant site (n = 1)	The study design is a 'before and after' study therefore there is no separate comparator arm. Company funded study

	Netherlands, Belgium, France and UK)		in urinary incontinence episodes per day or voids per day or reduction to <8 voids per day). Change in Quality of life (ICIQ-OABqol score; ICIQ-UI Short Form)** Patient satisfaction** Adverse events Number of explantations (with reasons)	In UUI test responders, leaks were reduced from 8.3 (± 0.8) per day at baseline to 1.8 (± 0.5) per day ($p < 0.0001$). In test responders with UF, voids were reduced from 14.3 (± 1.1) per day at baseline to 8.0 (± 0.47) per day $p < 0.0001$. Devices were explanted from 2 people between 6 and 12 months due to lack of efficacy	was resolved with reprogramming. Lead migration (n = 1) occurred between 3 and 6 months post-implant. Procedure-related serious adverse event: Infection at the IPG site (n = 1); device explanted after 3 weeks.	
Blok (2019c), unpublished manuscript; 2 year results Blok (2019b), 2 year results (published conference abstract & poster) were identified by	As above	As above	As above at 2 years	**Of the initial test responders (n=34), those who responded to therapy at:** **2 years:** 79% (n=27) **Symptom reduction** In test responders with UUI, leaks per day reduced from 8.3 (±0.8) at baseline to 1.7 (±0.5) at	21 device related AEs in 13 people (26%) over 2 years. 8 occurred within 2 weeks of implantation. Undesirable or uncomfortable stimulation: 13 events in 10 people	

the EAC after the original literature searches Before and after study				2 years (80% reduction, p < 0.0001). In test responders with UF, mean voids per day reduced from 14.3 (±1.1) at baseline to 7.3 (±0.4) at 2 years (p < 0.0001). Devices were explanted in 4/51 people (8%) due to lack of efficacy, but this total included only 1 initial test responder (1/34; 3%).	(20%), resolved with reprogramming. Pain at neurostimulator implant site: n = 1 Lead migration: n = 1 Lead fracture: n = 1 Explantation at 2 years: n = 7/51 (14%): • Infection at incision site: 1 • Lack of efficacy: 4 • High impedances: 1 MRI scan: 1 (device had not yet been approved for MR scan)	
UF – urinary frequency, UUI – Urge urinary incontinence, UI – Urinary incontinence, ICIQ-OABqol - Institut Català d'Investigació Química overactive bladder quality of life (questionnaire)						

** See results of this outcome in table 3 of the assessment report.

Summary of economic evidence

The company included 19 published studies in its submission, none of which was an economic evaluation of the Axonics device. The EAC judged these studies as falling outside the scope of the evaluation hence all the studies were excluded. The EAC's search did not identify any economic studies on Axonics. The EAC noted that the company's search strategy for the economics was comprehensive.

The EAC noted that one of the studies reported by the company was conducted in the UK (Freemantle et al.2016). This study assessed the cost effectiveness of onabotulinumtoxinA versus supportive care in the treatment of overactive bladder. Some costs and assumptions for the provision of SNM were included in the supportive care arm of this study.

The EAC stated that there was one economic model reported (Noblett et al. 2017) that compared rechargeable with non-rechargeable neuromodulation devices. Although it did not consider the Axonics SNM system and was not set in the UK, Noblett et al. (2017) is a cost-consequence model with quarterly progression between three health states (on SNM therapy, discontinuation of therapy and death). The EAC concluded from its quality assessment of Noblett et al. (2017) study that the main limitations include poor reporting of data sources and difficulty finding model data within the referenced papers. Noblett (2017) concluded that in a US setting the rechargeable neurostimulator may result in cost savings in overactive bladder treatment, due to a reduced need for replacement devices.

De novo analysis

The company submitted a Markov model with a 3-month cycle, comparing the rechargeable Axonics and the non-rechargeable Interstim devices. The model was an adaptation of the Noblett (2017) study to a UK setting. The model considers 3 health states - on SNM therapy (either rechargeable or non-rechargeable); off SNM therapy (discontinuation) and dead. The model does

not use typical Markov trace where calculations are presented for each health state. Instead each parameter is described separately, and all costs summed up. Patients move between states based on transition probabilities: mortality and per-cycle therapy discontinuation. The time horizon of the model was set to 15 years with scenarios including a 30-year time horizon. Costs arising after the first year were discounted at 3.5% per annum.

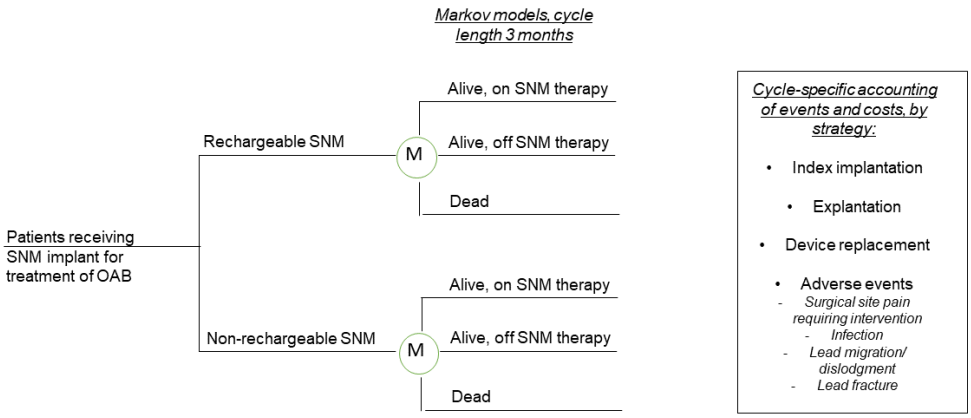

Figure 1 Model structure from company's submission

The key assumptions made by the company include

- Effectiveness and discontinuation between rechargeable and non-rechargeable device are the same
- Differences in device lifetimes leads to a reduced need for rechargeable device replacement and a reduction in procedure related adverse events
- There are no differences in testing procedures and test outcomes prior to full implantation of SNM device.

The EAC identified additional assumptions, details of which are listed in table 5 of the assessment report.

Model parameters

The clinical parameters for the model were sourced from the literature. Most clinical parameters and their distributions were obtained from the Insite study, Noblett et al.(2016).

Discontinuation rates for the first year were sourced from Noblett 2016 and those for subsequent years were taken from Chughtai (2015). The company applied these rates to both arms of the model. The EAC did not agree with the company's interpretation of Chughtai (2015) and amended discontinuation rates from 6% to 12.5%. As an alternative to applying the same discontinuation rates to both arms, the EAC used discontinuation rates derived from two-year results of the RELAX OAB study for the Axonics arm.

The company included 4 types of adverse events in its submission (surgical site infection, surgical pain, lead migration and lead fracture). The EAC noted that the company obtained the probability of surgical site infection from a mixed cohort of patients which is outside the scope (Brueseke (2015). Data on surgical pain was based on treatment at revision surgery and explantation surgery (Noblett 2016). The EAC used data from the ARTISAN SNM study for these parameters. The EAC judged that applying rates for lead migration, dislodgement and fracture to only the initial implant procedure was inappropriate. Expert advice confirmed that adverse events relating to leads can occur throughout the lifetime of the device. The EAC used lead migration data from the ARTISAN study. A full description of model parameters is described in section 7.2.2 of the assessment report.

Values for gender distribution, InterStim technology lifetime, and frequency of programming were from other sources, Suskind et al. (2013), Cameron et al. (2013), Freemantle et al. (2016). Updated clinical parameters used by the EAC are captured in table 6 of the assessment report.

Costs and resource use

Costs included were the technology costs, direct cost of implanting and managing the device and costs due to adverse events. The technology costs

(device and accessories; excluding VAT) of both rechargeable and non-rechargeable device were obtained from NHS Supply Chain. All procedures have an associated cost from the National Schedule of reference costs.

Table 2: Resources required during each procedure.

	Tined Lead (TL) Introducer Kit	Implanted Pulse Generator (IPG)	Tined leads (TL)	Charger	Percutaneous Nerve	Trial Stimulator	Tined Leads (TL) extension	Patient remote
Testing	✓		✓		✓	✓	●	✓
Initial implant procedure	✓	✓	✓	●				✓
Replacement due to infection	✓	✓	✓					
Replacement due to pain	✓	✓	✓					
Replacement due to battery depletion		✓						
Lead revision	✓		✓					
Lead replacement	✓		✓					
Required replacement of Charger System at 7.5 years				●				
Required replacement of Patient Remote at 7.5 years								✓
✓ required for both devices; ● required for rechargeable device only								

The EAC observed calculation errors in the company's model and made changes to correct VAT adjustment and inflation calculations. Other errors rectified by the EAC include cumulative discontinuation correction and an update for comparator device cost. Details of some of these changes are summarised in the table below

Table 3: The EAC's revision to model inputs

Parameter	Company value	EAC value	Source / comment
Initial implantation procedure and followup			
Implantation procedure	£3,531	£1,947	LB79Z, Insertion of Neurostimulator for Treatment of Urinary Incontinence. Changed from inpatient to daycase.
Device cost - InterStim	[redacted]	[redacted]	NHS Supply Chain
Device cost - Axonics	£9,660	Unchanged	NHS Supply Chain
Follow-up	£105	Unchanged	WF01A (Consultant led attendance, Urology, follow-up)
Battery replacement and routine equipment changes			
Battery replacement procedure	£672	£670	AA57A Minimal Intracranial Procedure, 19 years and over (day case)
Device cost - InterStim	[redacted]	[redacted]	NHS Supply Chain
Device cost - Axonics	£7,000	Unchanged	NHS Supply Chain
Patient programmer: InterStim	[redacted]	[redacted]	NHS Supply Chain
Patient programmer: Axonics	£500	Unchanged	NHS Supply Chain
Charger, Axonics	£560	Unchanged	NHS Supply Chain
Initial implantation procedure and followup			
Device removal (no replacement)	£2,379	£2,372	AA54C Intermediate Intracranial Procedures, 19 years and over, with CC Score 0-1 (day case)
Re-programming - complex	£112	£111	AA57A, General Surgery, Minimal Intracranial Procedure, 19 years and over (outpatient)
i.v. antibiotic treatment (4 wks.)	£5,232	£5,216	WH07B Infections or Other Complications of Procedures, with Multiple Interventions, with CC Score 0-1
Lead revision	£1,500	£1,495	LB80Z Insertion of Neurostimulator Electrodes for Treatment of Urinary Incontinence (day case)
Device cost - InterStim	[redacted]	[redacted]	NHS Supply Chain
Device cost - Axonics	£2,575	Unchanged	NHS Supply Chain
Healthcare costs for patients who are off-therapy			
Cost of incontinence (continence pads), per week	£8	£8	Per NICE CG 171 economic analysis, 2013
Cost of GP surgery consultation	£37	£38	PSSRU 2018, assumption per NICE CG 171
Frequency of GP visits per year in patients who discontinued therapy	6.0	6.0	Assumption per NICE CG 171 econ analysis
Testing costs, not used in submitted model, see Appendix G			
PNE, day case	£1,499	£1,495	HRG LB80Z
Device cost - InterStim	[redacted]	[redacted]	NHS Supply Chain

Parameter	Company value	EAC value	Source / comment
Device cost - Axonics	£475	Unchanged	NHS Supply Chain

Stage 1 tined lead implantation,	£1,500	£1,495	LB80Z Insertion of Neurostimulator Electrodes for Treatment of Urinary Incontinence (day case)
Stage 2 tined lead implantation,	£1,500	£1,495	
Device cost - InterStim	[redacted]	[redacted]	NHS Supply Chain
Device cost - Axonics	£2,575	Unchanged	NHS Supply Chain
Replacement interval for remote control and charging system (years)			
Patient remote, Non-rechargeable (yrs.)	15.0	Unchanged	
Patient remote, Rechargeable (yrs.)	7.5	Unchanged	
Charging System, Rechargeable (yrs.)	7.5	Unchanged	

Further adjustments made by the EAC to the model include applying day case costs rather that inpatient costs and modelling lead migration or fracture throughout the entire model rather than only in the initial cycle.

Results

The EAC judged that despite several changes made to the company's model, both the company's model and the EAC base case show that Axonics remained cost saving at 15 years. The company's base case result shows that Axonics has a total cost saving of £6,038. The EAC's revised base case analysis also shows that Axonics is cost saving with an increased saving of £6,273. Table 12 in the assessment report shows base case results from the company's de novo model and the EAC's revision of the company's model.

A tornado diagram was created by the EAC based on the company's clinical parameters used in its one-way sensitivity analysis. The diagram shows that the device replacement period was a key driver of cost savings (see figure 3 in the assessment report). The tornado diagram was repeated for the EAC's base case with the addition of device costs and varying each arm separately. The EAC notes that most high and low ranges were unchanged but based on EAC assumptions new ranges were chosen for a few parameters that had changed significantly. The timing of device replacement, the device cost and programming visits had the most impact on the results (see figure 4 in the

assessment report). The EAC explored the impact of varying expected lifetime until device replacement, results of the analysis show that Axonics become cost saving in the EAC's base case when the device lifetime preceding replacement is just under 6 years (see figure 5 and table 15 of the assessment report for more details).Scenario analysis done by the EAC showed that at a 10-year time horizon, Axonics is slightly more cost saving because 3 comparator devices would have been used (see table 16 of the assessment report for more details).

5 Ongoing research

The EAC did not identify any ongoing studies. ARTISAN SNM is due to complete in June 2020 and RELAX-OAB in February 2022.

6 Issues for consideration by the Committee

Clinical evidence

- The value proposition of this technology lies in its extended battery life. A lack of long-term data means that the potential advantages of this technology over the non-rechargeable SNM technologies has not been demonstrated clinically.

- There is a lack of comparative data between the Axonics device and the non-rechargeable comparator. This makes it difficult to validate claims of equivalent clinical effectiveness.

- A technical assessment is presenting the available company technical reporting on battery longevity, MRI compatibility and lead migration. To what extent will the technical evidence address the uncertainties in the clinical evidence on long-term clinical outcomes and clinical equivalence?

- Apart from the adverse events presented in the current evidence base, are there other side effects or adverse events that may occur as a result of having a rechargeable implant for 15 years? Would battery replacement be significantly more difficult due longer-term implantation?

- With the choice of a rechargeable and non-rechargeable SNM device at the same point in the clinical pathway, what clinical considerations inform the choice of device a refractory OAB patient gets?

- Considering that OAB is more common in women, how suitable is the Axonics device for women who intend getting pregnant in the future and what are the likely risks to the developing baby?

Cost evidence

- An assumption of equivalent clinical effectiveness between Axonics and the non- rechargeable device has been made without a direct comparison between both technologies. Has clinical equivalence been proven to support this assumption?

- The key cost driver of the cost savings associated with the use of Axonics SNM is the longer length of time between device replacements. Does the evidence support the extended battery life and less frequent replacements of the device?

7 Authors

Tosin Oladapo, Technical Analyst

Lizzy Latimer, Technical Adviser

NICE Medical Technologies Evaluation Programme

January 2020

Appendix A: Sources of evidence considered in the preparation of the overview

A Details of assessment report:

Poole R, Dale M. Morgan H, Ryczek E, Cohen B, Carolan-Rees G MT417 Axonics sacral neuromodulation system for bladder control in people with symptoms of overactive bladder, November 2019.

B Submissions from the following sponsors:

- Axonics Modulation Technologies, Inc.

C NICE guideline on Urinary incontinence and pelvic organ prolapse in women: management

NICE guidance on Sacral nerve stimulation for urge incontinence and urgency-frequency

NICE clinical guideline on Lower urinary tract symptoms in men: management

D References

Please see page 57 of the EAC assessment report and page 55 of the company submission for lists of references

Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Ased Ali, Consultant Urological Surgeon, Mid Yorkshire Hospital NHS Trust

Nicholas Fletcher, Urology Surgical Care Practitioner, Salford Royal Hospital

Chris Harding, Consultant Urological Surgeon, Newcastle-upon-Tyne Hospitals NHS Foundation Trust

Karen Nugent, Senior Lecturer, University of Southampton

Nikesh Thiruchelvam, Consultant Urologist, Cambridge University Hospitals NHS Trust

- Experts noted that optimal lead placement is dependent on experience of the operator. There was no agreement as to whether using curved stylets improved placement accuracy.
- Experts agreed that most patients have a new IPG implanted during the same procedure for removing an old one.
- No expert was aware of patients who had the device and had undergone MRI
- Experts stated that leads are checked before battery change.
- Experts noted that studies assessing SNM effectiveness could be confounded by subjective definition of improvement rates, patient's ability to record and give good history of symptoms, physiological factors and concomitant use of medication.

Appendix C: Comments from patient organisations and results of patient survey

Advice and information was sought from patient and carer organisations. One patient and carer organisation responded:

Bladder Health UK

- OAB is challenging to manage and causes withdrawal from social interaction for many patients. Elderly people with OAB are at risk of falls while getting up at night. Some patients have OAB associated with nocturia and this causes chronic fatigue and limits ability to carry out day to day activities.

Additional information was sought on the perceived benefits and disadvantages of rechargeable SNM devices; the experience during replacement surgery; and any concerns with having an SNM device implanted for 15 years:

- A non-rechargeable device has a limited lifespan. Uncertainty about whether the battery is running out is a source of worry to patients.
- Time to replacement of the non-rechargeable device may be a couple of months and this could mean patients return to using indwelling catheters or self-catheterisation which exposes them to an increased risk of infection.
- The replacement procedure for a SNM device can be uncomfortable
- Following surgery patients take a week off work to recover

Some of the concerns highlighted include, having a full awareness of rules that apply when one has an SNM and suitability of the device for women who may want to get pregnant in the future and the potential risk to the developing baby. Further concerns relate to potential difficulties that may occur when trying to replace the battery of an implant that has been in the body for a long time.

Patient survey

The PIP team at NICE sent out a patient questionnaire through clinicians in the NHS to patients who have had Axonics SNM implanted for symptoms of OAB.
Seven patients responded to the survey. The respondents considered Axonics to be beneficial in reducing symptoms of OAB, reducing urge incontinence and leakage, improving quality of life and reducing travel.

Regarding the effect of Axonics on how quickly symptoms resolve, one respondent noted that symptoms resolved within 2 months another respondent stated that there was an 80% improvement in their symptoms from baseline.
Respondents highlighted the surgical procedure, device related pain, limited ability to lift heavy items or inability to over stretch as the disadvantages of having the device.

Four respondents stated that they needed no further procedure to replace or adjust the device, whereas 3 respondent had further procedures. The timing for reprogramming varied among respondents from 6 weeks to 6 months.

Four respondents noted that their symptoms were managed by Axonics alone while 2 said they required conservative methods alongside Axonics. One respondent had drug therapy in addition to the Axonics device.

Appendix D: decision problem from scope and claimed benefits.

Population	People with symptoms of overactive bladder for whom conservative therapy and drug treatment have failed or are not suitable.
Intervention	Axonics Sacral Neuromodulation System
Comparator(s)	• Other sacral neuromodulation systems
Outcomes	The outcome measures to consider include:

	Primary outcomes Responder rate (% of patients who experience 50% or more reduction in their leaks compared to baseline) Level of reduction in overactive bladder symptoms such as average daily number of urgency leaks The number of surgical interventions to replace SNM devices and the risks associated with these procedures Time to battery depletion Ease of use of device Procedure related infection rates Incidence of therapeutic failure Improvement in quality of life including pain and discomfort **Secondary outcomes** Explantation rate due to MRI Time to revision surgery Level of patient and carer satisfaction Device-related adverse events	
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which may include scenarios in which different numbers and combinations of devices are needed.	
Subgroups to be considered	Slim people with lower than average BMI and a paucity of subcutaneous buttock fat are likely to benefit from a smaller device.	
Special considerations, including those related to equality	Urinary incontinence is associated with the protected characteristics of age, disability, sex and pregnancy. The device is contraindicated in people who cannot operate the device, which could include people with physical or cognitive impairment.	
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristics?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure MTAC will have relevant information to consider equality issues when developing guidance?	No
Any other special considerations	Not applicable.	

The benefits to patients claimed by the company are:

- Reduced number of repeat surgeries to replace the device and a reduction in the associated risks.
- Reduced pain and discomfort given the smaller size of the implant compared to previous similar devices.
- More time in optimal therapy range due to automatic adjustment of the therapy.
- Improved user experience.

The benefits to the healthcare system claimed by the sponsor are:

- Reduced number of surgical interventions
- Reduced cost of therapy

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

SCOPE

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

1 Technology

1.1 Description of the technology

The Axonics sacral neuromodulation (SNM) system (Axonics Modulation Technologies, Inc.), delivers sacral nerve stimulation therapy through a stimulator implanted subcutaneously in the upper buttock.

The stimulator generates electric pulses and is designed to operate on constant current which allows automatic adjustment of stimulation current. Lead electrodes implanted through corresponding sacral foramen transmit these pulses from the stimulator to the sacral nerves that control the bladder. The stimulator is powered by a rechargeable battery with an expected life span of at least 15 years, which is claimed to be longer than comparator non-rechargeable SNM devices. The device is programmed by a clinician.

A handheld remote control activates the stimulator, adjusts the stimulation amplitude, and checks the battery status. A wireless charger, attachable to the skin over the implanted stimulator is used to charge the stimulator. It is claimed that the battery needs a recharge every 1-2 weeks for 30 minutes to 1 hour.

Before permanent implantation, a trial is done for a few weeks to evaluate the efficacy of therapy in improving symptoms. The trial involves inserting a thin temporary wire near the sacral nerves in the lower back. The wire is connected to an external stimulator which sends stimulation to the nerves. A bladder diary is used before and after the procedure to assess improvement in

symptoms. Axonics SNM is MRI compatible and is claimed to be smaller than existing non-rechargeable SNM devices.

NICE has published a Medtech innovation briefing on this technology.

1.2 Relevant diseases and conditions

The Axonics SNM system is intended for use in the treating symptoms of overactive bladder, specifically in people for whom conservative therapy and drug treatment have failed or are not suitable.

The bladder and urethra are parts of the lower urinary tract which store and expel urine. These activities are regulated by both the central and peripheral nervous systems. Lower urinary tract symptoms have several causes including overactive bladder syndrome of unknown origin or other functional bladder disorders.

Lower urinary tract dysfunction may relate to impaired urine storage and /or bladder emptying resulting in symptoms such as overactive bladder syndrome (including urinary urge incontinence and/or symptoms of urgency-frequency). Urinary urge incontinence is a strong urge to urinate which is followed by an involuntary loss of urine. People who have urinary urge incontinence may also experience urgency-frequency (a need to pass urine more frequently than usual).

It is estimated that the prevalence of overactive bladder in the UK is 19% (Milsom et al. 2002).

1.3 Current management

NICE's guidelines on urinary incontinence and pelvic organ prolapse in women and lower urinary tract symptoms in men recommend initial management of symptoms with conservative methods (such as lifestyle interventions, behavioural techniques and physical therapies) or drug treatment. When conservative methods and drug treatment fail, investigation to assess detrusor overactivity is recommended. If detrusor overactivity exists, botulinum toxin type A can be injected into the bladder wall. The use of

botulinum injection may be associated with a need for clean intermittent catherisation or the use of temporary indwelling catheters.

If a patient is unwilling to accept the possible risk of catherisation with botulinum injection or if botulinum injection fails, NICE guideline recommends that, percutaneous sacral nerve stimulation should be offered[1]. NICE's interventional procedures guidance on sacral nerve stimulation for urge incontinence and urgency-frequency also suggests SNM is an option for people who have not responded to conservative management or drug treatment. Alternative invasive treatment options include bladder reconstruction (augmentation cytoplasty) and urinary diversion[2].

SNM involves applying an electric current to the sacral nerve believed to be responsible for communication between the bladder and the brain.

1.4 Regulatory status

The Axonics SNM system received a CE mark as a class III medical device in June 2016 for the treatment of urinary retention, symptoms of overactive bladder and chronic faecal incontinence

1.5 Claimed benefits

The benefits to patients claimed by the company are:

- Reduced number of repeat surgeries to replace the device and a reduction in the associated risks.
- Reduced pain and discomfort given the smaller size of the implant compared to previous similar devices.
- More time in optimal therapy range due to automatic adjustment of the therapy.
- Improved user experience.

[1] NICE NG123 Urinary incontinence and pelvic organ prolapse in women: management
[2] NICE NG123 Urinary incontinence and pelvic organ prolapse in women: management

The benefits to the healthcare system claimed by the sponsor are:

- Reduced number of surgical interventions
- Reduced cost of therapy

2 Statement of the decision problem

Population	People with symptoms of overactive bladder for whom conservative therapy and drug treatment have failed or are not suitable.
Intervention	Axonics Sacral Neuromodulation System
Comparator(s)	• Other sacral neuromodulation systems
Outcomes	The outcome measures to consider include: Primary outcomes • Responder rate (% of patients who experience 50% or more reduction in their leaks compared to baseline) • Level of reduction in overactive bladder symptoms such as average daily number of urgency leaks • The number of surgical interventions to replace SNM devices and the risks associated with these procedures • Time to battery depletion • Ease of use of device • Procedure related infection rates • Incidence of therapeutic failure • Improvement in quality of life including pain and discomfort Secondary outcomes • Explantation rate due to MRI • Time to revision surgery • Level of patient and carer satisfaction • Device-related adverse events
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which may include scenarios in which different numbers and combinations of devices are needed.
Subgroups to be considered	Slim people with lower than average BMI and a paucity of subcutaneous buttock fat are likely to benefit from a smaller device.

Special considerations, including those related to equality	Urinary incontinence is associated with the protected characteristics of age, disability, sex and pregnancy. The device is contraindicated in people who cannot operate the device, which could include people with physical or cognitive impairment.	
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristics?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure MTAC will have relevant information to consider equality issues when developing guidance?	No
Any other special considerations	Not applicable.	

3 Related NICE guidance

Published

- NICE guideline 123 (2019). Urinary incontinence and pelvic organ prolapse in women: management.
- NICE interventional procedures guidance 536 (2015 currently being updated). Sacral nerve stimulation for idiopathic chronic non-obstructive urinary retention.
- NICE clinical guideline 97 (2010 updated 2015). Lower urinary tract symptoms in men: management.
- NICE interventional procedures guidance 64 (2004). Sacral nerve stimulation for urge incontinence and urgency-frequency.
- NICE clinical guideline 148 (2012). Urinary incontinence in neurological disease: assessment and management

4 External organisations

4.1 Professional organisations

The following societies have been alerted to the availability of the draft scope for comment:

- British Society of Urogynaecology
- British Association of Urological Surgeons
- Neuromodulation Society of the United Kingdom and Ireland
- British Association of Spinal Cord Injury Specialists

4.2 Patient organisations

NICE's Public Involvement Programme contacted the following organisations for patient commentary and alerted them to the availability of the draft scope for comment.

- Bladder and Bowel UK
- Bladder Health UK
- ERIC, The Children's Bowel & Bladder Charity
- International Children's Continence Society
- Urostomy Association
- Urology User Group Coalition

NICE National Institute for Health and Care Excellence

Adoption report: MTG Axonics sacral neuromodulation system for bladder control in people with symptoms of overactive bladder

Summary – for first meeting

Adoption levers

- Battery life of 15 years compared with standard sacral neuromodulation (SNM) which is around 5 years. This means fewer surgical procedures for battery replacement
- Small device requiring minimal incision
- Same care pathway as for the standard non-rechargeable SNM device
- Additional treatment option for patients
- MRI compatible unlike the standard non-rechargeable SNM device.

Adoption barriers

- Clinical confidence about:
  - whether the battery will last as long as it is claimed
  - long term performance
  - the evidence of effectiveness for the Axonics device specifically
- Training requirement for nurse specialist in programming the device.

1 Introduction

The adoption team has collated information from healthcare professionals working within NHS organisations 3 of whom have experience of using the Axonics rechargeable sacral neuromodulation (SNM) system.

This adoption report includes some of the adoption considerations for the routine NHS use of the technology.

2 Contributors

The adoption team spoke to 4 NHS urology specialists; 2 consultant urological surgeons, 1 urology surgical care practitioner and 1 consultant urogynaecologist / uro-neurologist. The Axonics system has been adopted recently at 1 of the sites represented by 2 contributors.

3 Use of sacral neuromodulation and the Axonics SNM systemin practice

Contributors have been inserting sacral neuromodulation (SNM) in NHS practice since 1999/2000. It is offered following all appropriate tests to rule out other conditions (such as diabetes, cancer, kidney stone), to eligible patients in line with NICE guidelines on urinary incontinence and pelvic organ prolapse in women and lower urinary tract symptoms in men. SNM is offered to eligible men and women with overactive bladder. It was noted that this condition is more common in women. Two contributors said the proportion of patients with overactive bladder who would have failed previous care pathway steps and therefore be considered for SNM would be very low with one estimating 5-10%.

Sacral neuromodulation is inserted at specialist centres. The Axonics SNM system had been adopted by 1 NHS trust represented by 2 contributors who had inserted 6 devices at the time of writing.

When a patient with overactive bladder is at the invasive intervention stage of the care pathway, botulinium toxin is usually tried first and if this is not effective or acceptable to the patient SNM will then be considered. Botulinium toxin is available in all urology services. Patients therefore have access to this treatment without waiting for a referral to a specialist centre.

A permanent sacral neuromodulation device for a urology condition is inserted by a urologist or urogynaecologist in an operating theatre with fluoroscopy equipment. The procedure can be done as a day case but involves a general anaesthetic. There is no difference in the insertion procedure between the Axonics system and the standard non-rechargeable SNM device (InterStim II, Medtronic).

Following the procedure nurse specialists usually have the responsibility for programming the device and making changes to programs as required. The service will keep the patient under their care whilst the device is in place.

There was no difference to the current care pathway anticipated for the adoption of the Axonics system.

Contributors reported the lifespan of the battery for the standard non-rechargeable SNM device was, on average, 5 years (range 3.5 – 7 years). The device setting the patient uses strongly influences battery life. In 75% of battery replacement procedures, just the battery is replaced. The remaining 25% would require replacement of leads as well. A patient's lifestyle can be related to the incidence of faulty leads. One contributor explained that patients with SNM are advised against any activity which jolts the lower back. This includes horse riding, water skiing, skiing and mountain biking.

4 Reported benefits

The potential benefits of adopting the Axonics SNM system, as reported to the adoption team by the healthcare professionals using SNM technologies are:

- Battery life of 15 years compared with the standard non-rechargeable SNM device which is around 5 years. This means fewer surgical procedures for battery replacement (which involves an operation requiring general anaesthetic)
- Smaller device requiring a minimal incision
- Same care pathway as for the standard non-rechargeable SNM device
- Additional treatment option for patients
- MRI compatible unlike the standard non-rechargeable SNM device.

5 Insights from the NHS

Clinician confidence/acceptance

All contributors said that there is a lack of evidence about the long-term performance of the device and in particular they are unsure whether the battery will actually last

as long as it is claimed. One contributor wanted to see more evidence on the effectiveness of the Axonics system specifically.

Trial

Prior to permanent implant of SNM, patients are offered a trial. A successful trial is considered a 50% improvement in symptoms however, this is a guide and is subjective, with individual assessment of success or improvement. One contributor said that 50% of patients will have a successful trial. Contributors reported that until recently a trial kit had not been available from the Axonics company.

The site who currently implant the Axonics system purchase the standard non-rechargeable SNM device trial kit for all patients because they believe trail kits from both companies are the same. The trial system is inserted in clinic under a local anaesthetic by a urology surgical care practitioner. The single use disposable battery is external to the patient. After 2 weeks the trial leads and battery are removed.

Patient selection and Patient choice

The patient selection criteria are the same as for the standard non-rechargeable SNM device and in line with NICE guidance. However, the Axonics system is MRI compatible and therefore clinicians would recommend it for people expected to need an MRI. The trust that offers the Axonics system alongside the standard non-rechargeable SNM device, show patients both devices and explain the differences. Device selection is down to patient choice and over half have selected the Axonics system. Reasons patients did not choose this system included the lack of information about long term use and the need to recharge regularly reminding them they have a device in place.

Follow up

The follow up for the Axonics system is the same as for the standard non-rechargeable SNM device. Follow up varies between sites but commonly involves a post operative appointment with a nurse specialist (supported by a consultant for complex cases) at 4 weeks. A further nurse specialist appointment at 3 to 6 months and then 6 monthly to one yearly if stable. Patients are given the nurse specialists' phone numbers and may attend clinics more frequently if they need advice or

support. The frequency that a healthcare professional is required to re-programme the device is patient dependent.

The trust who have adopted the Axonics system do not switch it on until 4 weeks after the procedure. This lets the discomfort of the incision site ease (the programming device has to be attached to the battery which sits under the incision site). This is the same as their care pathway for the standard non-rechargeable SNM device.

One of the main reasons for regularly checking the standard non-rechargeable SNM device at a review appointment is to predict how much battery life is remaining. The Axonics battery has a claimed 15-year lifespan which could reduce the number of times patients have to attend hospital for a battery check.

Training and support

There is no additional training required for insertion of the Axonics system for clinicians familiar with standard non-rechargeable SNM devices. The representative from the company attends theatre for each insertion and this requires forward planning to ensure availably for all involved. This may be an additional step in the pathway compared with the standard non-rechargeable SNM device with an experienced clinician and the company representative is no longer required.

Training is required for programming the device and this is normally the responsibility of the nurse specialists. The Axonics company representative will attend the programming appointments and support the nurse specialist as required.

The company are confident that they have capacity to meet any increasing demands for training and support arising from increased adoption.

Commissioning and procurement

All sites inserting SNM for urology conditions are specialist centres. NHS England will routinely commission sacral nerve stimulation for overactive bladder in accordance with the criteria outlined in their clinical commissioning policy. Since April 2013 NHS England has been responsible for commissioning in line with this policy on behalf of the population of England. The company said that most NHS trusts

source the Axonics device from NHS supply chain through the a new nationwide system for purchasing and supplying High-Cost Tariff-Excluded Devices (HCTED) used in specialised services (zero cost model).

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Medical technologies guidance

MT417 Axonics sacral neuromodulation system for overactive bladder

Company evidence submission

Part 1: Decision problem and clinical evidence

Company name	**Axonics Modulation Technologies, Inc.**
Submission date	September 11, 2019
Regulatory documents attached	CE certificates Declaration of conformity ISO 13485 certificate Instructions for use
Contains confidential information	Yes

Contents

1 Decision problem

	Scope issued by NICE	Variation from scope (if applicable)	Rationale for variation
Population	People with symptoms of overactive bladder for whom conservative therapy and drug treatment have failed or are not suitable.	None	n/a
Intervention	The Axonics Sacral Neuromodulation System	None	n/a
Comparator(s)	Other sacral neuromodulation systems	None	n/a
Outcomes	The outcome measures to consider are: Primary outcomes: • Responder rate (% of patients who experience 50% or more reduction in their leaks compared to baseline) • Level of reduction in overactive bladder symptoms such as average daily number of urgency leaks • The number of surgical interventions to replace SNM devices and the risks associated with these procedures • Time to battery depletion • Ease of use of device • Procedure related infection rates • Incidence of therapeutic failure • Improvement in quality of life including pain and discomfort Secondary outcomes: • Explantation rate due to MRI • Time to revision surgery • Level of patient and carer satisfaction Device-related adverse events	None	n/a
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which may include scenarios in which different numbers and combinations of devices are needed.	None	n/a

Subgroups to be considered	Slim people with lower than average BMI and a paucity of subcutaneous buttock fat are likely to benefit from a smaller device.	None	n/a
Special considerations, including issues related to equality	Urinary incontinence is associated with the protected characteristics of age, disability, sex and pregnancy. The device is contraindicated in people who cannot operate the device, which could include people with physical or cognitive impairment.	None	n/a

2 The technology

Give the brand name, approved name and details of any different versions of the same device (including future versions in development and due to launch). Please also provide links to (or send copies of) the instructions for use for each version of the device.

Brand name	**Axonics Sacral Neuromodulation (SNM) System**
Approved name	Axonics Sacral Neuromodulation (SNM) System
CE mark class and date of authorisation	Class III Medical Device first approved on June 3, 2016

There is only one version of each of the product references approved to date.

Version(s)	Launched	Features
Enter text.	Enter text.	Enter text.
Enter text.	Enter text.	Enter text.
Enter text.	Enter text.	Enter text.
Enter text.	Enter text.	Enter text.
Enter text.	Enter text.	Enter text.

What are the claimed benefits of using the technology for patients and the NHS?

Claimed benefit	Supporting evidence	Rationale
Patient benefits		
Reduced number of repeat surgeries to replace the device and a reduction in the associated risks.	Product label approved for a minimum of 15 years life in the body, confirmed by testing data, literature describes 4.4 years life for the existing product, lists adverse events associated with repeat surgeries	A longer-lived system reduces the need for surgical procedures and their associated adverse events.
Reduced pain and discomfort given the smaller size of the implant compared to previous similar devices.	Literature describes a reduced rate of pain over the implant in patients implanted with a smaller implant than with the existing implant	A smaller implant positioned subcutaneously causes less pain over the implant site in patients.
More time in optimal therapy range due to automatic adjustment of the therapy.	Constant-current design of the Axonics system versus a voltage-controlled existing system, literature supporting patient preference and more sustained efficacy with constant-current devices	A constant-current system automatically adjusts to changes in tissue impedance and corrects stimulation to maintain optimal therapy, unlike a voltage-controlled system that requires reprogramming.
Improved user experience.	Design of a wireless Patient Remote, a Charging System with long intervals between charges, a touch screen, colour Clinician Programmer, literature describing patient satisfaction.	All elements of the Axonics system were designed to simplify use of SNM therapy for patients and physicians so that it is optimally delivered.
System benefits		
Reduced number of surgical interventions.	Product label approved for a minimum of 15 years life in the body, confirmed by testing data, literature describes 4.4 years life	A longer-lived system reduces the need for surgical procedures and their associated adverse events that

	for the existing product.	can also lead to revision surgery.
Reduced cost of therapy.	Product label approved for a minimum of 15 years life in the body, confirmed by testing data, literature describes 4.4 years life for the existing product. Similar prices for both products and procedures (NHS)	A longer-lived system reduces the need for surgical procedures and their associated costs, thereby reducing the overall cost of SNM therapy for the system.
Cost benefits		
Reduced number of surgical interventions.	Product label approved for a minimum of 15 years life in the body, confirmed by testing data, literature describes 4.4 years life for the existing product.	A longer-lived system reduces the need for surgical procedures and their associated adverse events that can also lead to revision surgery.
Reduced cost of therapy.	Product label approved for a minimum of 15 years life in the body, confirmed by testing data, literature describes 4.4 years life for the existing product. Similar prices for both products and procedures (NHS)	A longer-lived system reduces the need for surgical procedures and their associated costs, thereby reducing the overall cost of SNM therapy for the system.
Sustainability benefits		
Reduced number of surgical interventions.	Product label approved for a minimum of 15 years life in the body, confirmed by testing data, literature describes 4.4 years life for the existing product.	A longer-lived system reduces the need for surgical procedures and their associated adverse events that can also lead to revision surgery.
Reduced cost of therapy.	Product label approved for a minimum of 15 years life in the body, confirmed by testing data, literature describes 4.4 years life for the existing	A longer-lived system reduces the need for surgical procedures and their associated costs, thereby reducing the overall

	product. Similar prices for both products and procedures (NHS)	cost of SNM therapy for the system.

Briefly describe the technology (no more than 1,000 words). Include details on how the technology works, any innovative features, and if the technology must be used alongside another treatment or technology.

SNM therapy is a well-established therapy for patients with Urinary and Faecal dysfunction. As of 2015, SNM had been used to treat 250,000 patients worldwide (Block, 2018). SNM is indicated for the treatment of urinary retention and the symptoms of overactive bladder, including urinary urge incontinence and significant symptoms of urgency-frequency alone or in combination, in patients who have failed or could not tolerate more conservative treatments. SNM is also indicated for the treatment of chronic faecal incontinence in patients who have failed or are not candidates for more conservative treatments.

SNM therapy involves the use of electrical pulses to stimulate the sacral nerves located in the lower back. It works through insertion of a lead percutaneously into the S3 foramen, and connection of the lead to a neurostimulator implanted in the upper buttocks area. It is performed by specialized urologists, urogynecologists or colorectal surgeons. The procedure is reversible and is a 2-step procedure. Prior to 'permanent' implantation of the neurostimulator, responsiveness is tested using a test period of treatment using an external stimulator (NICE, IPG64). This involves the use of a temporary wire electrode which is later removed, or the use of a tined lead or electrode which can be left in permanently and later attached to the Neurostimulator. A decision to proceed with a permanent implantation of the SNS device is made on the basis of the results of test stimulation. A patient is suitable for permanent implant if they report a significant useful clinical response to the test period of treatment (e.g. at least 50% improvement in symptoms recorded in the bladder diaries). This offers SNS a unique advantage over other surgical options, as the patient outcomes can be assessed before a commitment is made to the permanent procedure. The permanent implant of the SNS system is minimally invasive, and it provides sustainable symptom relief in carefully-selected patients thereby avoiding repeated treatment with botulinum toxin A, or irreversible surgery (see Section 3.2). In patients who have failed treatment with SNS or where removal of the device is necessary, the treatment is fully reversible, simply involving an explant of the implanted components. Unlike some alternative treatments, SNS does not preclude further treatment options nor does it pose a delay or waiting period before which further treatment can be prescribed.

In 1994, Medtronic obtained CE Mark for the first and only other SNM system (Interstim®) commercially available to date. While Interstim has proven to be safe and effective, technological limitations have hindered optimal delivery of SNM therapy on several fronts:

- SNM is a chronic therapy that needs to be continuously delivered to provide symptom relief over the lifetime of a patient. Interstim employs a primary cell battery that requires the device be explanted and replaced every 4-5 years (Cameron 2013). This represents significant – and unnecessary - costs for health insurances and risk for patients.
- The Interstim neurostimulator is not approved for full-body MRI (Magnetic Resonance Imaging) scans, which prompts explantation of the device in patients who need to receive an MRI, generating unnecessary burden and costs. It also precludes

patients that have an established need for MRI to be implanted and receive proper care for their urinary symptoms.

- The Interstim II neurostimulator is 14cc in size, which causes discomfort and pain at the implant site to some patients, sometimes requiring an additional surgical procedure to reposition or explant the neurostimulator.
- The Interstim neurostimulator uses constant-voltage therapy. This does not provide a constant amount of current as the tissue resistance changes during scarring, which can require an adjustment of stimulation to maintain efficacy through additional hospital visits.
- External components necessary to the therapy are complicated to use and require industry personnel to be operated. This support can sometimes be charged to hospitals through increased product price.

The Axonics SNM System was developed as a new method of SNM therapy to address the shortcomings of the Interstim system. The technology is protected by over 80 issued patents covering its many innovations. The system comprises the following elements:

1) Neurostimulator: a long—lived, rechargeable device approved for a minimum life of 15 years, that provides electrical pulses to stimulate the S3 sacral nerve.

2) Tined Lead or Electrode: a stimulation cable with four (4) contacts to provide stimulation, with tines to avoid migration, similar to the Interstim tined lead.

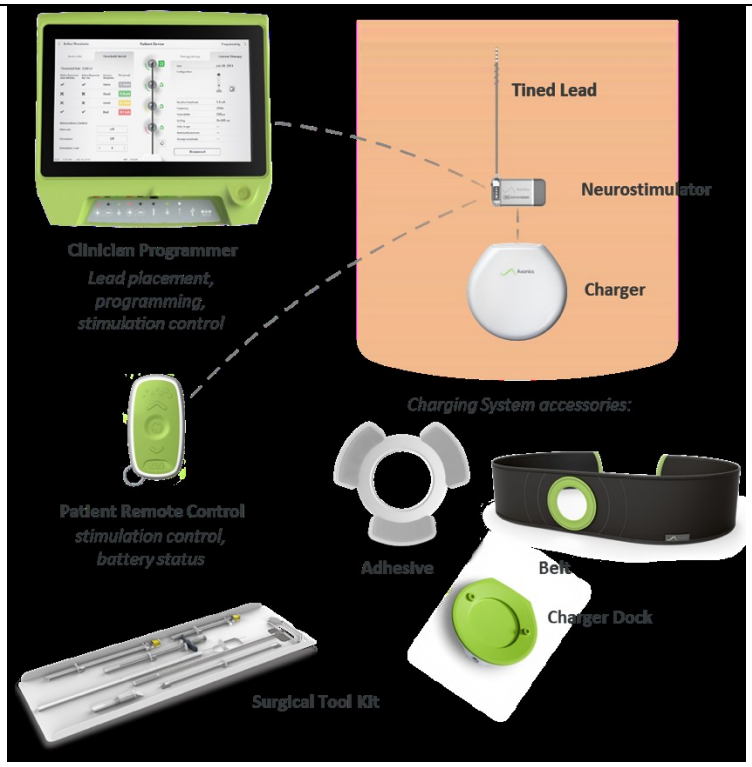
3) Patient Remote Control (RC): a portable handheld battery-operated device that uses radio-frequency (RF) signals to communicate with the neurostimulator. The RC allows the patient to observe and adjust stimulation levels, check neurostimulator battery charge level, and to turn the stimulation on or off.

4) Charger: a portable device used for transcutaneous charging of the neurostimulator through RF induction. The Charger can be held in place using a belt or an adhesive carrier. Charging is required every 1-2 weeks for 30 min to 1 hour on average, and is performed at home by the patient.

5) Clinician Programmer (CP): a portable tablet used by clinicians to program the implanted neurostimulator.

6) Trial System: includes an external stimulator that can be connected via an external cable to either the Tined Lead or temporary non-tined single contact lead for therapy evaluation prior to permanent implant.

7) Surgical tools kits: custom surgical tools allowing placement of leads onto the S3 sacral nerve and implantation of the Neurostimulator



The Axonics Neurostimulator has an approved (CE Mark) battery life of at least 15 years, which is 3 times longer than the current SNM standard of care Interstim II. The 15 years are open-ended, which means that if the Neurostimulator is still functional after 15 years it can continue to be used. Once the device stops working, it will require surgical replacement. External components such as the Patient Remote Control and the Charging System have a conservative life expectancy of at least 5 years, after which they may need to be replaced.

The Axonics SNM System was designed to address the shortcomings of the Interstim system. It offers the following innovations and improvements:

- A rechargeable battery: the Axonics battery embedded in the Neurostimulator is qualified by robust testing to function for at least 15 years, obviating the need for recurring surgical explant and replacement. This not only reduces exposure to adverse events associated with repeat surgeries for patients, but also generates a significant cost saving opportunity to the National Health System.
- An MRI-compatible implant: the Axonics Neurostimulator and Tined Lead are approved for patients who need to receive full-body MRI scans up to 3 Tesla, obviating the need to explant the device in patients who benefit from SNM therapy but need an MRI. This will also expand access to SNM therapy to patients with co-morbidities who would not be eligible to SNM today because of a need for repeated MRI scans due to a specific condition (such as chronic back pain).
- A miniaturized implant: the Axonics Neurostimulator is only 5cc in size, which is 60% smaller than Interstim II. This innovation is associated with a reduced risk of pain over the implant and its resulting need for revision surgery.

- Current-controlled stimulation: the Axonics Neurostimulator automatically adjusts output voltage based on tissue impedance, which provides more consistent therapy to reduce the need for stimulation adjustments, and therefore more time within the optimal therapy range.
- External components with enhanced functionality for both carer and patient: the Clinician Programmer was designed to provide a superior user experience and enhanced functionality with embedded stimulation capabilities and a proprietary algorithm generating programming recommendations so that hospital staff can manage patients without manufacturer support, in a time efficient manner. The Patient Remote Control is simplified to avoid loss of efficacy due to patients' inability to use it correctly.

The Axonics SNM System delivers equivalent SNM therapy to the Interstim system, as it uses the same stimulation parameters, has the same nerve target and is implanted through the same surgical procedure. It is intended to be prescribed and implanted by existing SNM experts in the UK, with limited training required on new features offered by Axonics. The use of the Axonics SNM System will not require any changes to the way SNM therapy is currently delivered in NHS hospitals. A limited training on the product specificities will be provided by Axonics staff to each user free of charge, as well as as-needed support during implant cases.

While none of the Axonics advancements were design to modify the therapy, they were designed to reduce adverse events, improve the user experience and reduce healthcare costs associated with SNM.

Briefly describe the environmental impact of the technology and any sustainability considerations (no more than 1,000 words).

The Axonics SNM System is a rechargeable system that offers an implant with a minimum of 15 years life in the body of patients, instead a 4.4 years life on average with the existing SNM system. This represents a 3-4 times longer time to replacement surgery for the implant, and therefore improves sustainability of SNM therapy and reduces its environmental impact. A 15+ years life is one of the longest approved life for an implantable medical device on the market today.

3 Clinical context

Describe the clinical care pathway(s) that includes the proposed use of the technology, ideally using a diagram or flowchart. Provide source(s) for any relevant pathways.

The following guidelines have been published in the UK on the treatment of Overactive Bladder and Sacral Neuromodulation:

- **NICE IPG64 – Sacral nerve stimulation for urge incontinence and urgency frequency (2004)**
    - Guidance indicates that available evidence on safety and efficacy of SNM for the treatment of urge incontinence and urgency frequency is adequate to support its use.
    - Guidance insists on the importance of patient selection and proper diagnosis. The procedure should be limited to patients who have failed conservative treatments, and who have positively responded to an external trial phase.

- **NICE CG171 – Urinary incontinence in women: the management of urinary incontinence in women (2013)**

- **NICE CG97 – LUTS (Lower Urinary Tract Syndrome) in Men (2013)**

- **NICE NG123 – Urinary incontinence and pelvic organ prolapse in women management (2019)**
    - These 3 guidelines detail the entire care pathway for women and men suffering from overactive bladder or urinary incontinence, from initial assessment to invasive surgical therapy.
        - Initial assessment includes history-taking and physical examination, assessment of pelvic floor muscle/prolapse, urine testing, bladder diaries, symptom scoring and quality of life assessment, cystoscopy and imaging.
        - First line therapies include lifestyle interventions, physical therapy, behavioural therapies, non-invasive stimulation and other conservative approaches.
        - Pharmacological treatment recommended includes antimuscarinics (oxybutynin, tolterodine or darifenacin), mirabegron, desmopressin. Likelihood of success and risks of adverse events should be discussed with patients before starting.
        - Second line therapies in case of drug failure or intolerance require discussion with an MDT (multidisciplinary team) to determine relevance of treatment.
        - Invasive procedures include botulinum toxin A injections, Sacral Nerve Stimulation (or Sacral Neuromodulation), augmentation cystoplasty and urinary diversion.

- **NHS England Clinical Commissioning Policy - Sacral Nerve Stimulation for Overactive Bladder (2016)**

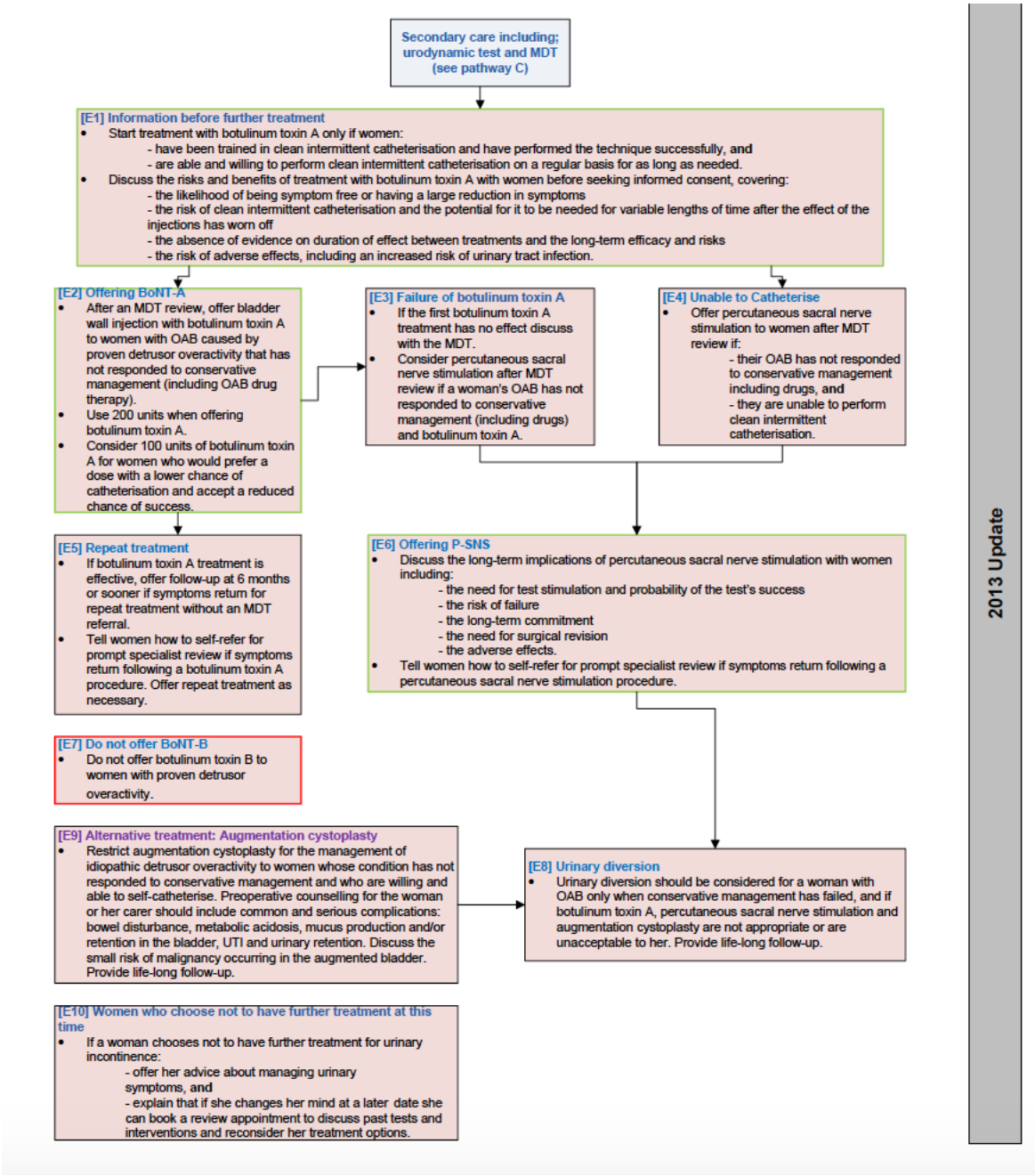
    - Policy reviews all available evidence and NICE guidelines on Sacral Nerve Stimulation for Overactive Bladder with the objective to outline clinical criteria which will identify patients most likely to benefit from SNM therapy.

    - Criteria for commissioning is as follows:
        - Confirmed diagnosis by urodynamics or an MDT
        - Failure to respond to conservative treatment including at least 2 anti-muscarinic drugs and a B3 agonist
        - Failure to respond or tolerate botulinum toxin injections
        - No known condition likely to necessitate MRI scanning

- **Medtech Innovation Briefing 164 – Axonics sacral neuromodultion System for overactive bladder and fecal incontinence (2018)**

    - Describes the advantages of the Axonics SNM System over existing SNM devices: rechargeability, longevity, small size and ease of use. MRI compatibility described is limited to 1.5T and 3T MRI head scans. **Labelling has now been expanded to 1.5T and 3T full body scans**.

This submission recommends the primary use of the Axonics SNM System in place of other existing SNM systems based on its advantages for patients, physicians and the NHS including device longevity and associated cost, size, ease of use and fully body MRI compatibility. Guidelines should be updated to reflect availability of a full body MRI-compatible SNM system, which can now be offered to patients with a known condition likely to necessitate MRI scanning. Otherwise existing guidelines as presented in CG171 are adequate (diagram for second line therapy represented below, full care pathway diagram provided as attachment to this submission).



Describe any training (for healthcare professionals and patients) and system changes that would be needed if the NHS were to adopt the technology.

Adoption of the Axonics SNM System by the NHS England will not impact the current pathway of care recommended by NICE for management of overactive bladder symptoms in women or the management of LUTS in men (NG123, CG171, CG97) or the way current services are organised or delivered. The longer battery life of the Neurostimulator will reduce or eliminate the need for replacement surgeries (every 15 years or more instead of every 4 to 5 years). Patients in need of an MRI scan will no longer need to be explanted. This will result in less patient management burden for physicians and more operating room time for other activities.

This submission however recommends the primary use of the Axonics SNM System in place of other existing SNM systems based on its advantages for patients, physicians and the NHS including device longevity and associated cost, size, ease of use and fully body MRI compatibility. Guidelines should be updated to reflect availability of a full body MRI-compatible SNM system, which can now be offered to patients with a known condition likely to necessitate MRI scanning.

The Axonics SNM System delivers equivalent SNM therapy to the existing Interstim system, as it uses the same stimulation parameters, has the same nerve target and is implanted through the same surgical procedure. It is intended to be prescribed and implanted by existing SNM experts in the UK, with limited training required on new features offered by Axonics. The use of the Axonics SNM System will not require any changes to the way SNM therapy is currently delivered in NHS hospitals. A limited training on the product specificities will be provided by Axonics staff to each user free of charge, as well as as-needed support during implant cases.

4 Published and unpublished clinical evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of articles identified in a systematic search.		1747
Number of articles identified as being relevant to the decision problem.		14
Of the relevant articles identified:	Number of published articles (included in table 1).	11
	Number of abstracts (included in table 2).	1
	Number of ongoing studies (included in table 3).	2

A literature search was performed using the PubMed database to identify published evidence on sacral neuromodulation systems. The search strategy is highlighted in Sections below, and the detailed search strategy is provided in appendix A. The search was performed to include all articles up to 31st July 2019. Published and unpublished evidence on sacral neuromodulation was analysed. Specific clinical evidence on the Sponsor's technology of rechargeable sacral neuromodulation was included, as well as evidence on other sacral neuromodulation systems. A single comparator was identified in the literature: the non-rechargeable Interstim® SNM system from Medtronic (referenced as "Interstim" further in the text).

A total of 11 published articles are used for the evaluation. Four articles were on the Sponsor's technology (the Axonics SNM System), and the remaining seven (7) articles were on comparative technology Interstim. A gray search was carried out to include conference presentations, abstracts and unpublished manuscripts on the Sponsor's technology. Unpublished data is only used for the Sponsor's technology. For comparator clinical evidence, only peer-reviewed, published evidence was considered appropriate.

List of relevant studies

In the following tables, give brief details of all studies identified as being relevant to the decision problem.

- Summarise details of published studies in table 1.
- Summarise details of abstracts in table 2.
- Summarise details of ongoing and unpublished studies in table 3.

- List the results of all studies (from tables 1, 2 and 3) in table 4.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

Table 1 Summary of all relevant published studies and unpublished follow-up results

1.a. Overview of all studies

Primary study reference	Study name	Population	Follow up (y=year, m=month)	Intervention	Control arm
Sponsor's technology					
Blok 2017a, Blok 2017b, Blok 2018	RELAX-OAB*	OAB (UI 73%, UF 98%)	3m, 3m, 6m & 12m*	Axonics	NA
McCrery 2019	ARTISAN-SNM**	OAB (UUI 100%)	6m**	Axonics	NA
Comparator technology					
van Kerrebroeck 2007	PAS	OAB (UI 63.2%; UF 16.4%; UR 20.4%)	5y	InterStim (Medtronic)	NA
Siegel 2015 †	InSite (Phase 1)	OAB (UI 63%; UF37%)	6m	InterStim (Medtronic)	Conventional medical treatment
Noblett 2016† and 2017; Siegel 2016; Siegel 2017	Insite (Phase 2)	OAB (UI – 27% or UF 22% or both 47%)	12m, 3y, 5y	InterStim (Medtronic)	NA
Amundsen 2018	Rosetta	OAB (UI)	2y	InterStim (Medtronic)	Botox

*Unpublished results at the latest follow-up at 2 years are available and presented in results

**Unpublished results at the latest follow-up at 1 year are available and presented in results

No studies comparing the Sponsor's intervention directly with the comparator were identified. No published studies identified were excluded from the analysis.

Data presented in Blok 2017a, Blok 2017b, Blok 2018, Blok 2019 (unpublished 2-year manuscript) is from the RELAX-OAB study. Data presented in McCrery 2019 and Lane 2019 (unpublished 1-year data presented at AUGS 2019 and SUFU 2020) is from the ARTISAN-SNM study. Data presented in Siegel 2015, Noblett 2016, Noblett 2017; Siegel 2016 and Siegel 2017 is from the InSite study.

1.b. Study design and methodology

Primary study reference	Study Design	External trial (Test) N	Permanent implant procedure N	Study Subjects	Age (years)	Female (%)
Sponsor's technology						
RELAX-OAB study (Blok 2017a, Blok 2017b, Blok 2018)	Prospective	Not performed	51	51	51	75%
ARTISAN-SNM study (McCrery 2019)	Prospective	Not performed	129	129	59.3	98%
Comparator technology						
PAS study (van Kerrebroeck 2007)	Prospective	163	152	152	44.7	87%
InSite study (Siegel 2015) †	RCT*	59	51	51	58	93%
InSite study (Noblett 2016† and 2017; Siegel 2016; Siegel 2017)	Prospective	340	272	272	57	92.10%
Rosetta study (Amundsen 2018)	Prospective	169	139	139	63.1	100%

In the PAS (Post-Approval Study) study (Van Kerrebroeck, 2007), most subjects were implanted with a device and surgical procedure that are not comparable to modern SNM therapy. In particular, a non-tined lead was used at the time, which was later demonstrated to be associated with significant lead migration issues that could lead to reduced efficacy (Spinelli et al., 2008; Sutherland et al., 2007; Thomson et al., 2010). This version of the comparator technology is not on the market anymore. Given these differences, this publication will not be included in the evidence

synthesis section for comparator technology evidence. All other studies on the comparator use the tined lead, and a comparable surgical procedure, and will therefore be included in the evidence synthesis section.

The Amundsen 2018 paper (Rosetta study) did not clearly define the definition used for calculating the responder rate. Per a previous paper on the same study (Amundsen 2016, reporting 6-month results), the responder rate definition represents individuals who had at least a 50% reduction in urgency leaks on **all** monthly diaries, not the diary at the specific follow-up visit, as with other studies in the literature. Given that this analysis method for calculating responder rates will result in an artificial underestimation of the actual responder rate, this publication was considered with caution in the evidence synthesis section.

All subjects in the Sponsor studies (RELAX-OAB and ARTISAN-SNM) studies were implanted with the Axonics system in a single, non-staged procedure, without use of an external trial. In contrast, in the comparator publications, only subjects that were responders to an external trial were implanted with the InterStim system. An external trial is typically 2-4 weeks long, at the end of which Trial responders are implanted with the permanent system, responders typically being defined as subjects that had clinically meaningful improvement in quality of life or at least 50% reduction in symptoms. All articles on the comparator technology present efficacy analysis in trial responders and do not include patients that failed the trial (i.e. trial failures).

In order allow comparisons with the comparator Interstim, data from the "Trial Responder" group, which was defined as subjects that had at least 50% reduction in their symptoms at 2 weeks or 1 month after implant, was analysed in studies specific to the Sponsor's Axonics system. All efficacy analyses in the RELAX-OAB and ARTISAN-SNM studies are available for both populations – "All implanted subjects" and "Trial Responders only". Safety analysis is conducted in all implanted patients.

The RELAX-OAB and InSite studies observed patients suffering from Overactive Bladder, presenting either urinary frequency symptoms, urinary urge incontinence symptoms or a combination. The ARTISAN-SNM and Rosetta studies observed patients suffering from urinary urge incontinence symptoms exclusively.

1.c. Detailed design and methodology for Sponsor's studies

ARTISAN-SNM	
Study name	**A**xonics Sac**R**al Neuromodula**TI**on **S**ystem for Urin**a**ry Urgency Incontinence Treatme**N**t: ARTISAN-SNM
Objective	Neuromodulation System as an aid in the treatment of the symptoms of UUI designed to gain pre-market approval in the United States.

Location	United States and Europe
Design	Single-arm, prospective, multi-center, unblinded pivotal study
Duration of study	2 years
Patient population	Urinary Urgency Incontinence (UUI)
Sample size	129 subjects
Inclusion criteria	• Diagnosis of UUI demonstrated on a 72-hour voiding diary defined as: -a minimum of four (4) leaking episodes associated with urgency, -at least 50% of all leaking episodes associated with urgency, and -at least one leaking episode each 24-hour period. • Greater than or equal to 6 months' history of UUI diagnosis • Positive motor response less than 4 mA on at least two (2) implanted electrodes during intraoperative test in the S3 (preferred) or S4 foramen • 21 years of age and older • No changes to current regimen of medications that affect bladder function for at least four (4) weeks prior to beginning the baseline voiding diary and baseline questionnaires • Willing and capable of providing informed consent

<table>
<tr><td>Exclusion criteria</td><td>

More than minimal level of stress incontinence or mixed incontinence with stress component likely to confound study outcome.
Current urinary tract mechanical obstruction (e.g. benign prostatic enlargement or urethral stricture)
Interstitial cystitis or bladder pain syndrome as defined by either AUA or EAU guidelines
History of any pelvic cancer
Current symptomatic urinary tract infection (UTI) or more than three (3) UTIs in past year
Any neurological condition that could interfere with normal bladder function, including stroke, epilepsy, multiple sclerosis, Parkinson’s disease, clinically significant peripheral neuropathy, or spinal cord injury (e.g., paraplegia)
Treatment of urinary symptoms with botulinum toxin therapy within twelve (12) months prior to SNM implant date
Treatment of urinary symptoms with tibial nerve stimulation within three (3) months prior to SNM implant date

</td></tr>
<tr><td>Intervention(s) (n =) and comparator(s) (n =)</td><td>Interventions (n=129)
No comparative treatments were used in the study</td></tr>
<tr><td>Baseline differences</td><td>Baseline demographics and clinical characteristics are presented below:
<table>
<tr><th colspan="2">Baseline demographics and clinical characteristics</th></tr>
<tr><td>Number of implanted participants</td><td>129</td></tr>
<tr><td>Age (years)</td><td></td></tr>
<tr><td>Mean (SD)</td><td>59.3 (13.0)</td></tr>
<tr><td>Median</td><td>61.0</td></tr>
<tr><td>Range</td><td>(21.0, 86.0)</td></tr>
<tr><td>Gender (n/N (%))</td><td></td></tr>
<tr><td>Female</td><td>127/129 (98)</td></tr>
<tr><td>Male</td><td>2/129 (2)</td></tr>
</table>
</td></tr>
</table>

	Race (n/N (%))	
	White	114/129 (88)
	Black or African American	9/129 (7)
	Other / Declined to answer	4/129 (3)
	Asian	2/129 (2)
	Duration of clinical diagnosis of UUI (years)	
	Mean (SD)	6.6 (7.0)
	Median	4.6
	Min, Max	0.5, 53.6
	Taking a concomitant medication to treat the condition (n/N (%))	40/129 (31)
	Current nocturia (n/N (%))	89/129 (69)
	Secondary diagnosis (n/N (%))[a]	
	Urinary frequency	65/129 (50)
	Stress incontinence	50/129 (39)
	Fecal incontinence	42/129 (33)[b]
	None	38/129 (30)
	Retention	2/129 (2)
	Type of previous surgical treatment (n/N (%))[a]	
	Sling procedure	33/129 (26)
	Botulinum toxin therapy	17/129 (13)
	Tibial nerve stimulation	17/129 (13)
	SNM external trial	9/129 (7)
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	• Proactive follow-up for up to 2 years. • Follow-up results at 6-months (published) and 1-year (unpublished) are available* • 3, and 6 subjects were lost to follow-up or exited study at 6 months and 1 year respectively	

Statistical tests	Statistical significance testing was performed using a one-sided binomial test for categorical variables and two-sided paired t-test or Wilcoxon signed rank test for continuous variables.
Primary outcomes (including scoring methods and timings of assessments)	3-day voiding diary was collected at baseline and follow-up visits. The primary effectiveness outcome was that the proportion of **all implanted subjects** that are Treatment Responders (i.e. subjects with ≥50% reduction in the number of urgency leaks) is greater than 50% at 6-months post activation. No external test assessment was performed prior to permanent implantation.
Secondary outcomes (including scoring methods and timings of assessments)	Responder rate in Trial/ Test responder subjects. Trial Responders were defined as patients demonstrating a 50% reduction in their symptoms during the first month following permanent implantation. No external trial assessment was performed prior to permanent implantation. Assessments used at baseline and follow-up visits: • Quality of life questionnaire: ICIQ-OABqol • Adverse events Assessments used at follow-up visits only: • Patient satisfaction with treatment (includes charging usability information)
RELAX-OAB	
Study name	Treatment of REfractory Overactive BLadder with the AXonics Sacral Neuromodulation System: RELAX-OAB
Objective	Post-market clinical follow-up (PMCF) study to confirm the safety and technical performance of the Axonics Sacral Neuromodulation (SNM) System as an aid in the treatment of the symptoms of overactive bladder (OAB)
Location	Europe
Design	Single-arm, prospective, multi-center, unblinded study with each subject serving as their own control
Duration of study	2 years
Patient population	Overactive bladder (Urinary incontinence, Urinary frequency)

Sample size	51
Inclusion criteria	• Diagnosis of OAB as demonstrated on a 3-day voiding diary defined as ≥ 8 voids/day, and/or a minimum of two involuntary urinary incontinence episodes in a 72-hour period • Positive motor response on at least two implanted electrodes during intraoperative test • 18 years of age or older • Failed, or are not a candidate for more conservative treatment (e.g., pelvic floor training, biofeedback, behavioral modification, oral pharmacotherapy) • No changes to current regimen of medications that affect bladder function for at least 4 weeks prior to beginning the baseline voiding diary
Exclusion criteria	• Primary stress incontinence or mixed incontinence where the stress component overrides the urgency component • Current urinary tract mechanical obstruction such as benign prostatic enlargement or urethral stricture • Interstitial cystitis or bladder pain syndrome as defined by either AUA or EAU guidelines • History of any pelvic cancer • Any significant medical condition that is likely to interfere with study procedures, device operation, or likely to confound evaluation of study endpoints • Current symptomatic urinary tract infection (UTI) or more than 3 UTIs in past year • Any neurological condition that may interfere with normal bladder function, including stroke, multiple sclerosis, Parkinson's disease, clinically significant peripheral neuropathy, or spinal cord injury (e.g., paraplegia) • Treatment of urinary symptoms with botulinum toxin therapy in the past 12 months • Treatment of urinary symptoms with tibial nerve stimulation in the past 3 months • Previously implanted with a sacral neuromodulation device or participated in a sacral neuromodulation trial

<table>
<tr><td>Intervention(s) (n =) and comparator(s) (n =)</td><td>Interventions (n=51)
No comparative treatments were used in the study</td></tr>
<tr><td>Baseline differences</td><td>
<table>
<tr><th></th><th>n</th><th>% (n/51)</th></tr>
<tr><td>Gender</td><td></td><td></td></tr>
<tr><td>Female</td><td>38</td><td>75%</td></tr>
<tr><td>Male</td><td>13</td><td>25%</td></tr>
<tr><td>Age</td><td>Years</td><td></td></tr>
<tr><td>Mean (Range)</td><td>51 (21–77)</td><td></td></tr>
<tr><td>Primary diagnosis</td><td></td><td></td></tr>
<tr><td>Urgency frequency</td><td>27</td><td>53%</td></tr>
<tr><td>Urinary urge incontinence</td><td>24</td><td>47%</td></tr>
<tr><td>Secondary diagnosis</td><td></td><td></td></tr>
<tr><td>Urgency frequency</td><td>12</td><td>24%</td></tr>
<tr><td>Urinary urge incontinence</td><td>10</td><td>20%</td></tr>
<tr><td>Stress incontinence</td><td>8</td><td>16%</td></tr>
<tr><td>Fecal incontinence</td><td>5</td><td>10%</td></tr>
<tr><td>OAB qualification in baseline diary</td><td></td><td></td></tr>
<tr><td>Both UF and UUI</td><td>36</td><td>71%</td></tr>
<tr><td>UF only</td><td>14</td><td>27%</td></tr>
<tr><td>UUI only</td><td>1</td><td>2%</td></tr>
</table>
</td></tr>
<tr><td>How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up</td><td>Proactive follow-up for up to 2 years.
Follow-up results at 3-months, 6-months, 1-year (published) and 2-years (unpublished) are available**
Total 8 subjects lost to follow-up or exited study at 1 year</td></tr>
<tr><td>Statistical tests</td><td>Statistical significance testing was performed using a one-sided binomial test for categorical variables and two-sided paired t-test or Wilcoxon signed rank test for continuous variables.</td></tr>
</table>

Primary outcomes (including scoring methods and timings of assessments)	Change in Quality of life questionnaire ICIQ-OABqol at 3 months
Secondary outcomes (including scoring methods and timings of assessments)	Assessments used at baseline and follow-up visits: • 3-day voiding diary - Responder rates in all implanted subjects and in Trial Responders (Definitions of Responder rates are the same as for ARTISAN-SNM) Assessments used at follow-up visits only: • Patient satisfaction with treatment (includes charging usability information)

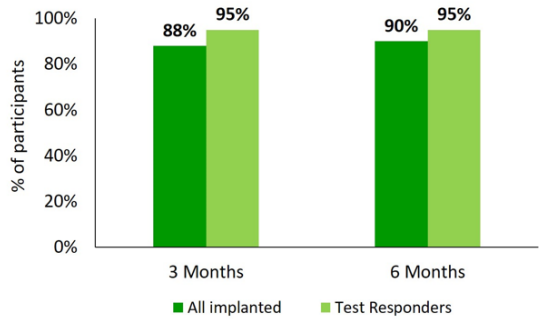
*For ARTISAN-SNM, 1-year follow-up data is unpublished; data to be presented at AUGS 2019 and SUFU 2020 is used for this purpose.

**For RELAX-OAB, 2-year follow-up data is unpublished; data from draft manuscript is used for this purpose.

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

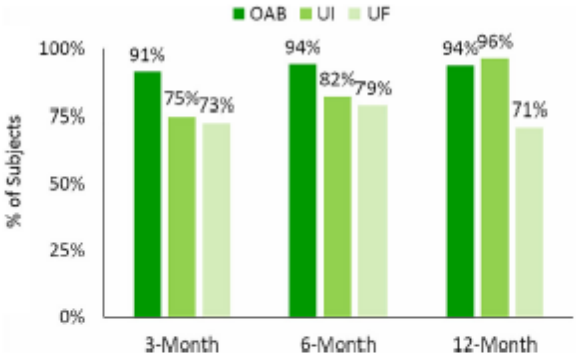
4.1. Results for Sponsor's studies

Study name		ARTISAN-SNM [McCrery 2019 (published up to 6-month follow-up); Lane 2019 (unpublished AUGS presentation and SUFU abstract up to 1 year data)]
Size of study groups	**Treatment**	Axonics rechargeable SNM system (n=129)
	Control	None
Study duration	**Time unit**	Follow-up (FU) available: up to 1-year
Type of analysis	**Intention-to - treat/per protocol**	Intention to treat
Outcome	**Name**	**Responder rate in all implanted subjects**
	Unit	**% of subjects (responders)**
Effect size (Primary endpoint)	**Value**	89.9% responder rate (at 6-month FU)
	95% CI	(83.4%, 94.5%)**
Effect size	**Value**	89.1% responder rate (At 1-year FU*)
	95% CI	(82.5%, 93.9%)**
Statistical test	**Type**	One-sided binomial test for responder rate >50%.
	p value	<0.0001
Outcome	**Name**	**Responder rate in all Trial Responder subjects**
	Unit	**% of subjects (responders)**
Effect size	**Value**	95% responder rate (at 6-month FU) 94% responder rate (at 1-year FU)
	95% CI	(88.8%, 98.0%) at 6-month FU** (87.7%, 97.5%) at 1-year FU **
Statistical test	**Type**	One-sided binomial test for responder rate >50%.
	p value	<0.0001

Additional results	**Responder rate results at different follow-up timepoints**	**Figure from McCrery 2019**  **Figure 2: Therapy responder rates in all implanted participants and Test Responder participants. UUI therapy response is defined as ≥50% reduction in UUI episodes at follow-up as compared to baseline. As-treated analysis is presented, where explanted or exited participants are considered as treatment failures. Test Responders are defined as participants that responded to the SNM therapy at 1 month.**
Other outcome	**Name**	**Average number of leaks in all implanted subjects**
	Unit	**Change/reduction in number of leaks (standard error)**
Effect size	**Value**	**Actual values:** Baseline: 5.6 ± 0.3; 6-month FU: 1.3 ± 0.2; 1-year FU: 1.4 ± 0.2 **Change in number of urgency leaks:** 4.3 ± 0.3 at 6-month FU; 4.2 ± 0.3 at 1-year FU **% leak reduction in all implanted subjects:** 77% at 6-month FU 75% at 1-year FU
	95% CI	(3.8, 4.9) at 6-month FU** (3.7, 4.8) at 1-year FU**
Statistical test	**Type**	Two-sided Wilcoxon signed rank test for paired observations for reduction from Baseline
	p value	<0.0001

Other outcome	**Name**	**Average number of voids for patients with at least 8 voids per day at baseline in all implanted subjects**
	Unit	**Change/reduction in number of voids (standard error)**
Effect size	**Value**	2.8 ± 0.3 at 6-month FU 2.7 ± 0.3 at 1-year FU
	95% CI	(2.3, 3.4) at 6-month FU** (2.1, 3.3) at 1-year FU**
Statistical test	**Type**	Two-sided Wilcoxon signed rank test for paired observations for reduction from Baseline
	p value	<0.0001
Other outcome	**Name**	**ICIQ-OABqol HRQL Score in all implanted patients**
	Unit	Change in Composite Score
Effect size	**Value**	34 points at 6-month FU 34 points at 1-Year FU [A 10-point improvement is considered clinically meaningful]
	95% CI	(29.9, 38.5) at 6-month FU** (30.2, 39.1) at 1-year FU**
Statistical test	**Type**	Two-sided Wilcoxon signed rank test for paired observations for reduction from Baseline
	p value	<0.0001
Other outcome	**Name**	**Patient satisfaction with treatment in all implanted patients**
	Unit	% of subjects

Effect size	**Value**	**At 6-month FU:** **93%** of all implanted subjects reported that they were satisfied with the treatment **92%** of all implanted subjects reported that they would undergo the therapy again with same expected results **98%** of all implanted subjects reported that charging frequency and duration is acceptable **95%** of all implanted subjects reported that charging is easy **At 1-year FU:** **93%** of all implanted subjects reported that they were satisfied with the treatment **92%** of all implanted subjects reported that they would undergo the therapy again with same expected results **96%** of all implanted subjects reported that charging frequency and duration is acceptable **89%** of all implanted subjects reported that charging is easy **100%** of all implanted subjects reported that they were able to charge their device**
	95% CI	NA
Study name		**RELAX-OAB** [Blok 2018 (published results up to 1 year follow-up); Blok 2019 (unpublished manuscript, up to 2y follow-up)]
Size of study groups	**Treatment**	Axonics rechargeable SNM system (n=51)
	Control	None
Study duration	**Time unit**	Follow-up (FU) available: Up to 2 years
Type of analysis	**Intention-to - treat/per protocol**	Per protocol
Other outcome	**Name**	**ICIQ-OABqol HRQL Score in Trial Responders (Primary endpoint: 3-month FU)**
	Unit	Change in Composite Score

Effect size	**Value**	27.3 points at 3-month FU (Primary endpoint) 21.1 points at 1-year FU 29 points at 2-year FU***
	CI	Not available [A 10-point improvement is considered clinically meaningful]
Statistical test	**Type**	Two-sided Wilcoxon signed rank test for paired observations for reduction from Baseline
	p value	<0.0001
Outcome	**Name**	**Responder rate in Trial responders**
	Unit	**% of subjects (responders)**
Effect size	**Value**	94% responder rate (at 1-year FU) 90% responder rate (at 2-year FU***)
	95% CI	Not available, see p-value instead
Statistical test	**Type**	One-sided binomial test for responder rate >50%.
	p value	<0.0001 (at 1-year and 2-year FU)
Additional results	**Responder rate results at different follow-up timepoints**	**Figure from Blok 2018**  **FIGURE 2** Therapy responder rates in Test Responders. Overall OAB therapy response was determined if subjects had a had a ≥50% reduction in voids, a ≥50% reduction in all leaks, or a reduction to less than 8 voids per day. UI therapy response was determined by a ≥50% reduction in all leaks, and UF therapy response was determined by a ≥50% reduction in voids or a reduction to less than 8 voids per day

Other outcome	**Name**	**Average number of leaks in Trial responders**
	Unit	**Change/reduction in number of leaks (standard error)**
Effect size	**Value**	**Actual values:** Baseline: 8.3 ± 0.8; 1-year FU: 1.8 ± 0.5; 2-year FU: 1.7 ± 0.5 **Change in number of leaks:** 6.6 ± 0.5 at 1-year FU 6.7 ± 0.5 at 2-year FU **% leak reduction:** 79% at 1-year FU 80% at 2-year FU
	95% CI	See standard error
Statistical test	**Type**	Two-sided Wilcoxon signed rank test for paired observations for reduction from Baseline
	p value	<0.0001
Other outcome	**Name**	**Average number of voids for Trial Responders with at least 8 voids per day at baseline**
	Unit	**Change/reduction in number of voids (standard error)**
Effect size	**Value**	**Actual values:** Baseline: 14.3 ± 1.1; 1-year follow-up: 8.0 ± 0.5; 2-year follow-up: 7.3 ± 0.4 **Change in number of voids:** 6.5 ± 1.1 at 1-year FU 7.0 ± 1.2 at 2-year FU **% void reduction:** 44% at 1-year FU 49% at 2-year FU
	CI	See standard error
Statistical test	**Type**	Two-sided Wilcoxon signed rank test for paired observations for reduction from Baseline
	p value	<0.0001

Other outcome	Name	Patient satisfaction with treatment in Trial Responders
	Unit	% of subjects
Effect size	Value	**At 1-year FU**, †** **91%** of Trial Responders reported that they were satisfied with the treatment **93%** of Trial Responders reported that they would recommend r-SN to a friend **100%** of Trial Responders reported that charging frequency and duration is acceptable **At 2-year FU***, †** **93%** of Trial Responders reported that they were satisfied with the treatment **90%** of Trial Responders reported that they would recommend r-SN to a friend **86%** of Trial Responders reported that charging frequency and duration is acceptable
	95% CI	NA

* Unpublished data from Lane et al. AUGS 2019 Conference presentation and SUFU 2020 abstract
** Unpublished company data from internal reports.
*** Unpublished data from Blok 2019 RELAX-OAB study 2-year FU manuscript draft.
† Given discrete variables with binary categorizations, a statistical test was not considered appropriate.

Based on the latest follow-up results of the ARTISAN-SNM and RELAX-OAB studies, the average leak symptom reduction is 78%, and the average improvement in ICIQ-OABqol composite score is 31.5 points.

Average void reduction is not calculated across the two studies since the ARTISAN-SNM study population did not enrol urinary frequency patients.

4.1. Results for Comparator's studies

The effectiveness of comparable non-rechargeable SNM systems for treatment of urinary indications of OAB is presented below.

All studies reported screening patients with a therapy "test period" using an external trial system before implanting the full SNM system. Test responders were defined as patients that had at least a 50% reduction in symptoms at 2-3 weeks. A full SNM system was implanted only in patients that were responders during the external test period.

Therapy responders were defined as patients with full SNM system implants that were responders to the treatment at long-term follow-up.

Three (3) studies (InSite, Rosetta, and PAS studies) on urinary dysfunction reported responder rates for clinical study patients and symptom reduction. Data from all three studies is reported in this Results section. Per reasoning provided above, the PAS study is not further used for evidence synthesis.

Responder rates

For UI, a responder rate was defined as patients with at least a 50% reduction in leaks as compared to baseline. Full continence, or dry patients, was defined as patients with no incontinence episodes on the follow-up visit diary. For UF, a responder was defined as patients with a 50% or greater reduction in voids as compared to baseline or less than 8 voids at follow-up.

All articles, except van Kerrebroeck 2007, reported outcomes for a “Completers” analysis which included “Test Responders” that were available at follow-up, and missing data imputations for patients missing at the follow-up visit was not performed.

Van Kerrebroeck 2007 performed analysis in patients that had completed the follow-up visit. Additionally, patients who exited the study due to an adverse event or lack of efficacy were considered unsuccessful and were assumed to return to baseline (i.e., they were assumed to be treatment failures). For patients that did not provide a follow-up dairy or missed the study visit for other reasons, the last observation carried forward was used to impute missing data.

Averages across articles are calculated for summarizing data. Only data from the latest follow-up was used for calculation of average responder rates/ symptom reduction. Averages are calculated when more than one article provided information on responder rate.

Study reference	Article reference	Follow-up duration	Patient population	Test responder rate (%)	Therapy responder rate (%)	Full continence rate (%)
Rosetta	Amundsen 2018	6m †	UUI	82	58*%-60**%	5*
		1y †	UUI	82	55*%	6*
		2y	UUI	82	50*	5*
InSite	Siegel 2017 †	1y†	OAB	85***	85	-
			UI	NA	79	45
			UF	NA	70	-
	Siegel 2017††	5y	OAB	85***	82	-
			UI	NA	76	45
			UF	NA	71	-

Study reference	Article reference	Follow-up duration	Patient population	Test responder rate (%)	Therapy responder rate (%)	Full continence rate (%)
PAS	van Kerrebroeck 2007¥	5y	UI	NA	58	NA
			UF	NA	40	-
			UR	NA	71§	-

NA: Not available in the article

† *Results for this follow-up are provided for comparative evidence synthesis analysis in later sections.*

†† *Since multiple articles were available on the InSite study (Noblett 2016, Noblett 2017, Siegel 2015, Siegel 2016, Siegel 2018), responder rate data is presented from the most recently published article with the longest-term follow-up (Siegel 2017).*
** Therapy responder rate was not provided in the text and is estimated from a graph provided in the article.*
*** Therapy responder rate at 6 months provided in previous article – Amundsen 2016*
****Test Responder rate is not provided separately for the UF and UI populations.*
§ *UF responder rate is calculated using criteria of a 50% or greater reduction in voids only, and criteria of less than 8 voids was not used*
¥*Minimum 3-day diary was required.*

The therapy responder rate for the OAB population, inclusive of both UI and UF populations, was 82% (Siegel 2017).

Using the latest follow-up durations, the average therapy responder rate for UI/UUI was 61.3% and for UF was 55.5%. Full continence was achieved on average by 25% of patients.

Article reference	Follow-up duration	Baseline value	Follow up value	Delta from baseline value (%)
Overactive Bladder (Urinary Incontinence)				
Insite study: Siegel 2018 (5y)	5 y	3.1 + 2.7*	NA	-2.0 (64.5%) *P<0.0001*
PAS study: van Kerrebroeck 2007 (5y)	5 y	9.6 ± 6.0	3.9 ± 4.0	-5.7 (59.3%) P<0.001
Rosetta study: Amundsen 2018	2 y	5.2 + 2.7	1.7	-3.5 (67.3%) P<0.001
Overactive Bladder (Urinary Frequency)				
Insite study:	5 y	12.6 ± 4.5*	NA	-5.4 (42.8%)

Article reference	Follow-up duration	Baseline value	Follow up value	Delta from baseline value (%)
Siegel 2018 (5y)				*P<0.0001*
PAS study: van Kerrebroeck 2007 (5y) ¥	5 y	19.3 ± 7.0	14.8 ± 7.6	-4.5 (23.3%)

NA: Not available
**Only data from the latest follow-up at 5 years is presented*
¥Minimum 3-day diary was required.

Quality of Life

Quality of Life assessment in OAB patients (urinary urge incontinence and/or urgency frequency) was reported in the articles on the InSite study. Quality of life was sustained in the patient population through 3- and 5-year periods as reported in Siegel 2016 and Siegel 2018. ICIQ-OABqol was used to assess the improvement in quality of life. A minimally important difference of 10 points from baseline to follow-up is considered as clinically significant improvement on the ICIQ-OABqol scale. Siegel 2018 reported that 84% of patients experienced improved quality of life 5 years after SNM implant.

Additionally, Siegel (2015) performed a randomized controlled trial comparison of SNM to standard medical therapy (SMT) and showed that the SNM group had significant improvements in quality of life versus the SMT group ($p<0.001$).

Amundsen 2018 assessed quality of life using the the Overactive Bladder Satisfaction of Treatment Questionnaire (OAB-SATq). The Overactive Bladder Questionnaire Short Form (OAB-SF) questionnaire ranges from 0 to 100, with higher scores on the symptom severity scale indicating greater severity of symptoms and higher scores on the quality of-life scale indicating better quality of life. The overall OAB-SF score in the SNM group changed from 35.7 at baseline to 77.4 at 2 years, an average improvement of 41.7 points.

5 Details of relevant studies

Please give details of all relevant studies (all studies in table 4). Copy and paste a new table into the document for each study. Please use 1 table per study.

RELAX study	
How are the findings relevant to the decision problem?	All data is specific to the Axonics SNM System and the population described in the decision problem. Outcomes reported include response rate, symptom reduction, adverse events, patient satisfaction
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes, reduced pain over the implant
Will any information from this study be used in the economic model?	Yes
What are the limitations of this evidence?	The study is a non-randomized study with no control arm.
How was the study funded?	Sponsored by Axonics Modulation Technologies, Inc. Controlled by a DSMB.

ARTISAN study	
How are the findings relevant to the decision problem?	All data is specific to the Axonics SNM System. Outcomes reported include response rate, symptom reduction, adverse events, patient satisfaction
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes: reduced pain over the implant, more time in optimal therapy range supporting increased efficacy
Will any information from this study be used in the economic model?	Yes
What are the limitations of this evidence?	The study is a non-randomized study with no control arm. The population described in the decision problem is partially represented only (UUI patients instead of OAB).
How was the study funded?	Sponsored by Axonics Modulation Technologies, Inc. Controlled by a DSMB.

InSite study	
How are the findings relevant to the decision problem?	All data is specific to the comparator Intertim system and the population described in the decision problem. Outcomes reported include response rate, symptom reduction, adverse events.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes, a higher pain over the implant rate is reported than in Axonics studies, as well as a lower response rate
Will any information from this study be used in the economic model?	Yes
What are the limitations of this evidence?	Responders at various endpoints are only calculated on the basis of patients attending follow-up visits. Patients lost to follow-up are not counted as failures.
How was the study funded?	Sponsored by Medtronic Ltd.

Rosetta study	
How are the findings relevant to the decision problem?	All data is specific to the comparator Intertim system. Outcomes reported include response rate, symptom reduction, adverse events.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes, a higher pain over the implant rate is reported than in Axonics studies, as well as a lower response rate
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	Responder definition does not correspond to standard definition found in other studies (a responder needs to have responded at ALL his visits). The population described in the decision problem is partially represented only (UUI patients instead of OAB).
How was the study funded?	Public funding

PAS study	
How are the findings relevant to the decision problem?	All data is specific to the comparator Intertim system and the population described in the decision problem. Outcomes reported include response rate, symptom reduction, adverse events.

PAS study	
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes, a higher pain over the implant rate is reported than in Axonics studies, as well as a lower response rate
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	Technology and procedure used in this study are not used anymore – were associated with a high rate of adverse events and are therefore not representative of current standard of care.
How was the study funded?	Medtronic Ltd.

6 Adverse events

Describe any adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude). Please provide links and references.

There were no MHRA reportable adverse events observed with commercial implants of the Axonics SNM System since launch in the UK on November 1, 2018. The Axonics SNM System received approval in the United-States on September 6, 2019, therefore there are no adverse events related to the product reported in the Maude database to date.

Describe any adverse events and outcomes associated with the technology in the clinical evidence.

All device- and procedure-related adverse events from the above studies is presented below.

Adverse events from Sponsor clinical studies

Adverse events list	**% Total subjects (Cumulative)**	
RELAX-OAB (n=51)	**1 year**	**2 year***
Uncomfortable Change in Sensation or Magnitude of Stimulation	20%	20%
Pain or irritation at INS site	2%	2%
Lead migration	2%	2%
Infection	2%	2%
Explant (all subjects)	6%	14%**
ARTISAN-SNM (n=129)	**6 months**	**1 year***
Uncomfortable Change in Sensation or Magnitude of Stimulation	5%	5%
Unintended Nerve Activation	0%	2%
Pain or irritation at INS site	2%	2%
Discomfort/heating during charging	0%	1%
Incisional Site Infection	1%	1%
Suspected Lead Migration	1%	1%
Other Adverse event	0%	2%
Explant	2%	3%***

*Unpublished data presented at conferences or in draft manuscript form
**This rate is 6% if Trial failures are excluded.
***This rate is <1% is Trial failures are excluded.

The most common device-related AE in the RELAX-OAB and ARTISAN-SNM studies was undesirable or uncomfortable stimulation (20%, and 5% respectively). These events were

resolved with reprogramming in all subjects. Pain at the implant site occurred in one subject (2% of all subjects) in both the studies. Eight (8) of the 21 AEs (38%) occurred during the initial two-week period after implant (unpublished Blok 2-year manuscript).

Adverse events in comparative SNM system studies

Adverse event list	**% of Total subjects**	
Insite study	**1 year**	**5 year**
	(Noblett 2016)	**(Siegel 2017)**
Undesirable change in stimulation	12.0%	22.0%
Implant site pain	7.0%	15.0%
Implant site infection	3.0%	3.0%
Surgical intervention due to AE	13.0%	30.9%
Surgical intervention due to battery replacement	NA	33.5%
Permanent explant	NA	19.1%
Lead fracture	1.0%	NA
Lead displacement	1.0%	NA
Other device-related AEs	NA	6.0%
PAS	**5 year (van Kerrebroeck 2007)**	
Device revision or replacement (includes revision or lead or INS)	23.7%	
Surgical intervention due to AE	39.5%	
Undesirable change in stimulation	27.0%	
Pain at implant site	19.7%	
Lead migration	3.3%	
Rosetta study	**2 years (Amundsen 2018)**	
Revision	2.9%	
Explant	10.0%	
Infection	2.9%	
Procedural pain	6.0%	

In the RELAX-OAB study, of all the device- and procedure-related AEs at 12 months post-implant, 50% and 77% occurred in the first 3 and 6 months respectively (unpublished company data). Siegel et al (2017) reported that, of the device- and procedure- related AEs occurring in the first 12 months, 56% and 79% occurred within 3 and 6 months respectively.

In commercial practice, Trial failures do not get a permanent SNM implant. Since the Sponsor studies implanted all patients regardless of their potential Trial outcome, an explant rate is calculated for Initiial successes only in the Sponsor studies, to be able to compare to studies on comparator technology (excluding the theoretical Trial failures). This revised explant rate for the Sponsor studies is in the range of 1%-4% at follow-up durations of 6 months and 2 years. The explant rate in comparator studies is in the range of 10-19% at follow-up durations of 2 years and 5 years respectively.

7 Evidence synthesis and meta-analysis

Although evidence synthesis and meta-analyses are not necessary for a submission, they are encouraged if data are available to support such an approach.

If an evidence synthesis is not considered appropriate, please instead complete the section on qualitative review.

If a quantitative evidence synthesis is appropriate, describe the methods used. Include a rationale for the studies selected.

Comparative analyses between the Sponsors technology (Axonics rechargeable SNM system) and the comparator technology (InterStim, non-rechargeable SNM System) are presented. Published and unpublished evidence is synthesized to provide a comparison of results across studies. When appropriate, methods used for data synthesis are described within each sub-section. When comparator data is not available, a non-comparative review/ analysis of only the Sponsor's system is provided.

Additionally, per reasoning provided above, the PAS study is not used for evidence synthesis.

One of the Scope outcomes (Number of device related AEs) is addressed with several sub-sections.

Report all relevant results, including diagrams if appropriate.

Efficacy and Quality of life

- Responder rates & Incidence of therapeutic failure

SNM systems are typically implanted in patients that respond to an external trial evaluation (i.e. Trial responders), while Trial failures are not implanted with a permanent SNM system. All efficacy analyses in the literature identified for the comparator are typically performed in the Trial responders' group only, and subjects that were Trial failures are excluded from the analysis. In the ARTISAN-SNM and RELAX-OAB studies, all subjects were implanted with the SNM system, without evaluation with an external trial. However, in order to be comparable with existing literature, a Trial Responders group was defined in each study. The Table below compares Trial responder rates across the different studies identified.

Typically, results are only reported in subjects that are available at follow-up (i.e. Completers analysis). This results in the analysis being performed in a smaller group of subjects, which may cause artificial inflation of the reported results. A conservative approach would be to consider lost to follow-up subjects as treatment failures.

In the ARTISAN-SNM study, subjects missing at follow-up were conservatively considered to be treatment failures.

The RELAX-OAB study and InSite study published articles present data in Completers group. A conservative case analysis was therefore performed for both these studies: all missing subjects, whether explanted or lost to follow-up, are assumed to be treatment failures for visits following their exit from the study.

The Table below presents reported responder rates and conservative case responder rates.

The Rosetta study is included in the comparative analysis, however, results from this study should be considered with caution, since the definition of responder rate was not clearly stated in the Amundsen 2018 paper.

Treatment Responder rates in Axonics clinical studies and SNM literature

Study/ Report	Intervention	Study Population (Number of Trial/Test Responders)	Treatment Responder Rates (Study-reported)*		Treatment Responder Rates (Conservative-case)**	
			6 months	12 months	6 months	12 months
ARTISAN-SNM	Axonics System	UUI (N=113)	95% (N=113)	94% (N=113)	95% (N=113)	94% (N=113)
RELAX-OAB	Axonics System	OAB† (n=34)	94% (N=34)	94% (N=32)	94% (N=34)	88% (N=34)
		UUI (N=28)	82% (N=28)	96% (N=26)	82% (N=28)	89% (N=28)
InSite	InterStim System	OAB (N=272)	80% (N=240)	85% (N=220)	71% (N=272)	69% (N=272)
		UI (N=202)	76% (N=190)	79% (N=173)	71% (N=202)	68% (N=202)
Rosetta	InterStim System	UUI (N=139)	58%¥-60¥¥% (N=139)	55% (N=135)	58% (N=139)	53% (N=139)

*Treatment Responder rates are reported in subjects available at follow-up visits.
**Treatment Responder rates are calculated by assuming conservative case outcome i.e. Treatment failure for subjects that were unavailable at follow-up visits
***Only UI responder rate is considered relevant for this comparative analysis.
† Includes UF subjects
¥ Per figure in Amundsen 2018; ¥¥ Per results in Amundsen 2016

As seen in the table above, the therapy responder rates reported in Sponsor's specific evidence on the Axonics system are higher (88%-94%) than the responder rates reported in comparator's literature (53%-68%). Even if the responder rate from Rosetta is not included in the analysis, the overall as-treated responder rate of the comparator studies is 68%. As stated in McCrery 2016, the high response rate seen in Axonics literature can explained by a combination of factors, which include the use of high-standard surgical techniques in the field during the clinical studies, a user-friendly remote control reducing risk of accidentally turning off stimulation, or the use of constant current stimulation. Indeed, The Axonics SNM

System is the only SNM system that delivers constant-current stimulation, while the comparator uses constant-voltage stimulation. Constant-current stimulation is a Neurostimulator built-in capability that automatically adjusts stimulation based on changes in tissue impedance. During the first weeks post implantation, the Tined Lead is encapsulated by adjacent tissue during scaring, which leads to an increase in tissue resistance (McCrery 2019). According to Ohm's law, this results in a reduction of the voltage delivered by a constant-voltage neurostimulator, which may contribute to sub-optimal stimulation of the nerve. Consequently, patients and physicians often need to adjust voltage to maintain proper stimulation of the nerve, by increasing current through reprogramming of their device. This can be performed by the remote control or sometimes requires an additional hospital visit. The constant-current capability of the Axonics SNM System maintains optimal stimulation of the sacral nerve through time and tissue impedance changes, providing more consistent activation of the target nerve and mitigating the need for reprogramming, thus providing optimal therapeutic benefit to the patient (Lettieri et al., 2015). Constant-current stimulation is a standard of care in other neuromodulation applications such as deep brain stimulation or spinal cord stimulation. It has been demonstrated in clinical literature that constant-current stimulation is directly related to optimal therapeutic outcomes (Lettieri et al., 2015), provides superior efficacy and has patient preference. This hypothesis should be further corroborated by additional long-term studies on the Axonics patient population.

The higher responder rate observed with the Axonics system constitutes evidence of average strength given the indirect comparison with the comparator and the absence of randomized controlled study comparing the two technologies.

- - Level of reduction in OAB symptoms

The Sponsor's studies reported an average of 78% reduction in leaks i.e. UUI/UI symptoms. The comparator InSite study reported an average of 64.5% reduction in UI symptoms. This level of symptom reduction is considered comparable between the Sponsor and the comparator studies (see previous sections for detailed results).

- Improvement in quality of life

As shared in sections above, quality of life was assessed using ICIQ-OABqol questionnaire. A 10-point improvement from baseline to follow-up is considered clinically meaningful. As detailed above, the Sponsors studies show an average of 31.5 points improvement in quality of life. Additionally, both the sponsors studies reported that over 90% patients were satisfied with their treatment.

Of the comparators, only Siegel reported on ICIQ-OABqol, and results were that 86% subjects showed at least 10 points improvement. Comparator's literature report similar improvements in quality of life.

The improvements in quality of life with both technologies are considered meaningful and equivalent.

Safety

- Time to battery depletion / Number of surgical interventions to replace SNM devices

The Axonics rechargeable Neurostimulator has a validated and approved life span of at least 15 years (CE mark, testing report available upon request). In comparison, the existing non-rechargeable SNM neurostimulator Interstim II has an average life span of 4.4 years (Cameron et al., 2013). Consequently, the Axonics Neurostimulator offers an increased longevity that expands the time between initial implantation and battery depletion, and therefore the time until surgical replacement.

The open-ended 15 years (15 years or longer – no limitation at 15 years) life span of the Axonics Neurostimulator has been validated through extensive testing based on industry standards. Life span evaluation is performed by accelerated charge/discharge cycles and assessment of their impact on the Neurostimulator performance through time, in particular its charging time (duration of a charge) or charging interval (time need between 2 charges). The Axonics Neurostimulator battery has been tested through a total of 1,000 charge/discharge cycles with less than 20% loss in performance. For an average charging interval of 2 weeks (charging every 2 weeks), this corresponds to 40 years of life. For an average charging interval of 1 week (charging every week), this corresponds to almost 20 years of life (1,000 cycles / 52 weeks = 19.2 years). The Axonics Neurostimulator also contains smart software technology that limits charging intensity for protection against early degradation. On this basis, Axonics conservatively obtained CE mark approval for an open-ended duration of 15 years.

The Axonics Tined Lead has also been validated for a 15 years life span based on the industry standard EN 45502-2-2:2008. Evaluation is performed through bending cycles simulating stress over time in an accelerated fashion. A 5 years conservative life span is anticipated for a lead resisting 47,000 bending cycles. The Axonics Tined Lead passed over 200,000 bending cycles, representing a life span of over 20 years. This data supported CE mark approval of the Axonics system for an open-ended life of 15 years.

These testing results are provided to NICE in confidentiality. Full testing report is available to NICE upon request.

Overall, it is expected the Axonics SNM System will not require a Neurostimulator replacement surgery over a period of 15 years post-implant, whereas the comparator Interstim II will require at least 3 replacement surgeries during this period of time. On a longer time scale, it is expected that the Axonics SNM System will need to be replaced a single time over 30 years, while the comparator Interstim II will require over 6 replacement procedures over the same period of time.

A surgical Neurostimulator battery replacement is associated with adverse events and bears risks linked to the procedure such as anaesthesia, pain, infection and antibiotics exposure (Noblett 2016). Expanding the time to surgical replacement of the Neurostimulator therefore reduces the anticipated rate of adverse events that a patient will experience after an SNM implant to benefit from the therapy. A reduced need for surgical replacements is also associated with a better economic profile for SNM therapy, both from

a hospitalization cost and from a product cost perspective (see Economic section for detailed evaluation).

- Device-related AEs & Procedure related infection rates & Number of Neurostimulator replacement surgical interventions and risks associated with these procedures

Detailed safety data from Axonics and the comparator's clinical literature are presented in Section 6.

As discussed in the section above, the Axonics SNM System has been approved for a device life of at least 15 years, while the comparator's average device life is of 4.4 years on average, after which surgical replacement is required. Consequently, over an average 20 years of therapy, an Axonics patient is anticipated to undergo a maximum of 1 replacement procedure between 15 and 20 years. In comparison, a patient implanted with the comparator technology is anticipated to undergo a minimum of 4 replacement procedures over 20 years: between 4 and 5 years, between 9 and 10 years, between 13 and 15 years, and between 17 and 20 years.

An increased number of implant procedures with the comparator technology is expected to increase the rate of device and procedure related AEs.

This assumption is corroborated by evidence from the literature that shows that majority of the adverse events (AEs) occurring in the first 12 months post-implant surgery occur during the first 3 and 6-months post-implant. For example, Siegel et al (2017) reported that, of the device- and procedure- related AEs occurring in the first 12 months, 56% and 79% occurred within 3 and 6 months respectively. Similarly, in the RELAX-OAB study, of the device- and procedure-related AEs at 12 months post-implant, 50% and 77% occurred in the first 3 and 6 months respectively. These AEs typically include undesirable change in stimulation, implant site pain, implant site infection. The Sponsor studies reported procedure-related infection rates in the range of 1-2%. The comparator studies reported procedure-related infection rate of approximately 3%.

These results demonstrate that lowering the number of repetitive implant surgeries with a longer-lived device can be expected to result in a lower rate of all device and procedure related adverse events.

Siegel 2017 reported that 33.5% of the subjects in the InSite study needed a replacement surgery due to battery depletion of the comparator at 5 years. In Axonics specific studies, 0% subjects have required a surgery for battery replacement at 2 years.

In MIB164 published by NICE in 2018, it was stated that most of the expert commentators' thoughts the longer battery life would provide the largest benefit to patients and lead to fewer revision surgeries. Fewer revision operations, as well as fewer outpatient follow-up visits and inpatient visits for implant site pain, were identified as potential system benefits.

- Device related AEs: Time to revision surgery

As discussed in previous sections, and per Cameron 2005, 100% of patients implanted with an Interstim system are anticipated to need a revision or explant surgery for Neurostimulator

replacement due to battery depletion within the first 4-5 years post-implant. In contrast, 0% of the patients implanted with the Axonics system are anticipated to need a Neurostimulator replacement surgery for at least 15 years post-implant.

Other reasons for revision or explant surgery, unrelated to Neurostimulator battery depletion, exist with both devices. These reasons include but are not limited to infections, pain at implant site, lead migrations, lead fractures, lack/loss of efficacy, subject choice and/or need for MRI. While lead migrations and lead fractures could have behavioural causes (e.g. heavy lifting, fall etc.), and are therefore expected to occur at a similar rate for both devices, the other causes, such as infection, and pain at implant site are related to the surgical procedure itself. A higher rate of Neurostimulator replacement surgeries is therefore expected to increase procedure-related adverse events such as pain at implant site and infection, which in turn can result in more revision or explant surgeries. Since the Axonics device is expected to have 0% Neurostimulator revision surgeries due to battery replacement over the first 15 years post-implant, the rate of explants arising from these procedure-related AEs (pain at implant site, infection etc.) is expected to be 0%.

Additionally, since the Axonics System has full-body MRI approval, the need for MRI should not be a cause of explant of the Axonics system. The need for MRI is on the other end still likely to be a cause of explant surgeries for the Interstim system (see further section dedicated to MRI explantation rate).

Due to all these reasons, over a span of 15 years, a lower number of explant or revision surgeries are expected with the Axonics system than with the Interstim system, and the time to revision surgery is expected to be longer with the Axonics system as compared to the Interstim system.

- Device related AEs: Rates of pain and discomfort

The Axonics SNM System includes a miniaturized Neurostimulator, that is 5cc in size, which is 60% smaller than the comparator neurostimulator Interstim II. Clinical evidence on the comparator reports pain/ discomfort rates of 15-19% at implant site at 5 years (Siegel 2017, Van Kerrebroeck, 2007). Sponsor's specific evidence reported pain at implant site for approximately 2% patients at various endpoints (Blok 2018; McCrery 2019). These results support the claim that a smaller sized device results in a lower rate of pain/discomfort at implant site. The combination of a lower number of repetitive implant surgeries with a miniaturized device reduces the anticipated rate of adverse events associated with SNM therapy.

In MIB164 published by NICE in 2018, it was stated by two expert commentators that the smaller implant size reduces the risk of device-related pain, as well as improve comfort.

- Explantation rate due to MRI

Existing SNM devices are only compatible with MRI scanners equipped with a head coil, and for scans of 1.5 Tesla only. The Axonics Neurostimulator and Lead have received CE mark for MRI scans with full body coil up of to 3 Tesla. It is the only SNM system approved for full body MRI scans and/or for 3 Tesla scans. It is estimated that today 69% of MRI scans are full body MRI scans (https://magnetic-resonance.org/ch/21-01.html). Therefore, the Axonics SNM System is the sole system available for patients eligible to SNM therapy who have an

identified need for repeated MRI scans (for instance patients suffering from chronic pain). Patients implanted with an SNM system not approved for full body MRI scans currently have to undergo surgical explantation of their device in order to be safely scanned. It is estimated that approximately 20% of SNM explants are due to a need for MRI (Lloyd et al., 2017, Peters et al., 2017). A full body MRI compatible SNM system prevents surgical risks and adverse events associated with an explant procedure such as anaesthesia, pain, infection or antibiotics exposure (see previous sections). Explants also require additional time in the operating room for physicians and burden to the hospital system, and eventually additional costs. Most explanted patients (90% - Lloyd et al., 2017) will not request a new implant, therefore preventing them from receiving appropriate care. Patients who chose to keep their SNM system and not undergo the MRI scan will not receive adequate diagnosis for their condition. A full body MRI compatible SNM system is therefore improving the patient care pathway by both expanding access to SNM therapy and reducing adverse events and costs of explant surgery.

Ease of use of device

- Clinician Programmer

The Axonics Clinician Programmer is a touch screen color tablet with built-in stimulation capabilities that test stimulation of the Tined Lead in the operating room and programs stimulation after implantation. It generates programming recommendations using a proprietary algorithm, and records patient information and stimulation history, such as the Neurostimulator. It communicates wirelessly with the Neurostimulator and Trial Stimulator, without the need for an antenna or communicator like the comparator's programmer (see below). It provides direct stimulation without the need for the Trial Stimulator as an intermediary during the procedure, as is required for the comparator. The Axonics Clinician Programmer was developed to improve ease of use for physicians, save time when managing patients and increase reproducibility of stimulation parameters among patients and hospitals.

Comparison of Axonics and Interstim Clinician Programmers

Axonics	Interstim
Wireless operation Communicates directly with INS (no antennas)	**Communicator needed** Requires Communicator to connect to INS
Algorithm provides programming recommendations	All patients provided same standard 7 programs
Delivers Test Stimulation	Communicates with ETS to deliver test stimulation via ETS

- Patient Remote Control

The Axonics Patient Remote Control allows adjustments in stimulation by the patient. It was design to be simple to understand and use, based on the limitations of the comparator's remote control. Firstly, it is a small and discrete device that fits on a key

chain, limiting the social impact of the therapy for patients who carry it. It has a broad, wireless range of communication with the Neurostimulator without the need for external antennas or other communicators, that can be used in a one-handed operation as opposed to the comparator's remote control that involves 2 separate elements to operate (Figure below). The Axonics Remote Control has no digital screen to limit patient use errors and is limited to 3 simple functions: 1) indicates when it is time to recharge, 2) increase or decrease stimulation, 3) switch programs during the test phase. The Axonics Remote Control has a minimum life span of 5 years upon daily use, and does not require special batteries to function, unlike the comparator's remote control.

In MIB164 published by NICE in 2018, it was stated by 1 commentator that older patients could benefit from the easy-to-use and compact patient equipment, and that it could reduce complexity for these patients and help improve their understanding of therapy.

Comparison of Axonics and Interstim Patient Remote Controls

Axonics	Interstim
One-handed operation Communicates directly with INS (no antennas)	**Two-handed operation** Requires Communicator to connect to INS
ETS: 2 programs INS: 1 program	7 programs
Non-rechargeable battery with open-ended life	Remote Control and Communicator must both be charged

- Charging System

The Axonics SNM System is the first rechargeable SNM System commercially available. Rechargeability of the Neurostimulator is what supports its extended life span of at least 15 years. The Axonics Charging System was designed to improve limitations of existing charging systems used for spinal cord stimulation and offers an improved experience to patients with a limited charging time of between 30 min and 2h, and an increased charging interval of up to 2 weeks. In the ARTISAN-SNM clinical study, 100% of all subjects were able to charge their device at 1-year. The duration of charging was acceptable for 96% of all subjects. 89% of all subjects reported that it was easy to recharge their SNM system.

In MIB164 published by NICE in 2018, it was stated by 1 commentator that patients have found the technology easy to master and the remote control simple to use. According to another, patients are happy with the system and have no issues recharging the device.

Explain the main findings and conclusions drawn from the evidence synthesis.

Axonics specific clinical literature as compared to comparator literature demonstrates strong evidence of safety and efficacy for the treatment of overactive bladder using sacral neuromodulation. Advantages of the Axonics rechargeable SNM system over the comparator SNM system (InterStim) include an improved safety profile (reduced rate of replacement surgeries, full-body MRI compatibility, smaller implant size), as well as superior ease of use for patients and physicians, and equivalent, if not superior efficacy. The cost of therapy is also improved over the comparator. Although higher efficacy was seen in the Sponsor's studies as compared to the comparator technology, these results should be corroborated by more studies. The Axonics SNM System does not introduce any new risks relating to adverse events as compared to the comparator SNM System.

Qualitative review

Please only complete this section if a quantitative evidence synthesis is not appropriate.

Explain why a quantitative review is not appropriate and instead provide a qualitative review. This review should summarise the overall results of the individual studies with reference to their critical appraisal.

Enter text.

8 Summary and interpretation of clinical evidence

Summarise the main clinical evidence, highlighting the clinical benefit and any risks relating to adverse events from the technology.

Axonics specific clinical literature demonstrates strong evidence of safety and efficacy for the treatment of overactive bladder using sacral neuromodulation. Advantages of the Axonics rechargeable SNM system over the comparator SNM system (InterStim) include an improved safety profile (reduced rate of replacement surgeries, full-body MRI compatibility, smaller implant size), as well as superior ease of use for patients and physicians, and equivalent, if not superior efficacy. The cost of therapy is also improved over the comparator. Although higher efficacy was seen in the Sponsor's studies as compared to the comparator technology, these results should be corroborated by more studies. The Axonics SNM System does not introduce any new risks relating to adverse events as compared to the comparator SNM System.

Briefly discuss the relevance of the evidence base to the scope. This should focus on the claimed benefits described in the scope and the quality and quantity of the included studies.

All evidence identified relevant to the scope was included in this submission. Further evidence is required to further assess some claimed benefits, in particular where no comparative evidence is available.

Identify any factors which might be different between the patients in the submitted studies and patients having routine care in the UK NHS.

The 90% therapy response rate, achieved in the entire cohort of 129 implanted participants (as treated) in the ARTISAN-SNM study, is one of the highest response rates reported in SNM literature. We hypothesize that this high response rate is due to a combination of factors, including Sponsor's technological superiority (constant-current system, simple patient remote), but also the adherence to strict and most recent guidelines for best implant techniques by the study investigators (McCrery 2019). This includes use of the curved stylet to optimize the placement of the tined lead, thereby potentially improving therapeutic outcomes.

Describe any criteria that would be used in clinical practice to select patients for whom the technology would be most appropriate.

n/a

Briefly summarise the strengths and limitations of the clinical evidence for the technology.

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.

9 References

Please include all references below using NICE's standard referencing style.

- **Axonics rechargeable SNM System – specific evidence on the technology**

  - Blok et al., Three month clinical results with a rechargeable sacral neuromodulation system for the treatment of overactive bladder – Neurourol.Urodyn. 2018 Feb;37(S2):S9-S16 *[provided with submission]*
  - Blok et al., Programming settings and recharge interval in a prospective study of a rechargeable sacral neuromodulation system for the treatment of overactive bladder – Neurourol.Urodyn. 2018 Feb;37(S2):S17-S22 *[provided with submission]*
  - Blok et al., A prospective, multicenter study of a novel, miniaturized rechargeable sacral neuromodulation system: 12-month results from the RELAX-OAB study – Neurourol Urodyn. 2019 Feb;38(2):689-695 - https://www.ncbi.nlm.nih.gov/pubmed/?term=A+prospective%2C+multicenter+study+of+a+novel%2C+miniaturized+rechargeable+sacral+neuromodulation+system%3A+12-month+results+from+the+RELAX-OAB+study
  - Blok et al., Two years outcomes of the treatment of overactive bladder with a rechargeable SNM System - unpublished manuscript *[attachment provided with submission]*
  - Lane et al., One-year outcomes of the Axonics® System for treatment of urinary urgency incontinence – SUFU 2020 abstract *[attachment provided with submission]*
  - Lane et al., Treatment of urinary urgency incontinence with the Axonics® miniaturized, rechargeable SNM system: Clinical outcomes of the ARTISAN-SNM pivotal study - AUGS 2019 presentation *[attachment provided with submission]*
  - McCrery et al., Treatment of Urinary Urgency Incontinence Using a Rechargeable SNM System: 6-month Results of the ARTISAN-SNM Study - J Urol. 2019 Jul 26 [Epub ahead of print] - https://www.ncbi.nlm.nih.gov/pubmed/?term=Treatment+of+Urinary+Urgency+Incontinence+Using+a+Rechargeable+SNM+System%3A+6-month+Results+of+the+ARTISAN-SNM+Study

- **Sacral Neuromodulation – Comparator evidence**

  - Amundsen CL, et al. Two-Year Outcomes of Sacral Neuromodulation Versus OnabotulinumtoxinA for Refractory Urgency Urinary Incontinence: A Randomized Trial. Eur Urol. 2018 Jul;74(1):66-73 - https://www.ncbi.nlm.nih.gov/pubmed/?term=Two-Year+Outcomes+of+Sacral+Neuromodulation+Versus+OnabotulinumtoxinA+for+Refractory+Urgency+Urinary+Incontinence
  - Noblett et al., Results of a prospective, multicenter study evaluating quality of life, safety, and efficacy of sacral neuromodulation at twelve months in subjects with symptoms of overactive bladder - Neurourol Urodyn. 2016 Feb;35(2):246-51 - https://www.ncbi.nlm.nih.gov/pubmed/?term=esults+of+a+prospective%2C+multicenter+study+evaluating+quality+of+life%2C+safety%2C+and+efficacy+of+sacral+neuromodulation+at+twelve+months+in+subjects+with+symptoms+of+overactive+bladder
  - Noblett et al., Detailed analysis of adverse events and surgical interventions in a large prospective trial of sacral neuromodulation therapy for overactive bladder patients - Neurourol Urodyn. 2017 Apr;36(4):1136-1139 - https://www.ncbi.nlm.nih.gov/pubmed/27491027
  - Siegel et al., Results of a Prospective, Randomized, Multicenter Study Evaluating Sacral Neuromodulation With Interstim Therapy Compared to Standard Medical Therapy at 6-Months in

Subjects With Mild Symptoms of Overactive Bladder, Neurourol. Urodynamics 34:224–230 (2015) - https://www.ncbi.nlm.nih.gov/pubmed/24415559

- Siegel et al., Three-year Follow-up Results of a Prospective, Multicenter Study in Overactive Bladder Subjects Treated With Sacral Neuromodulation - Urology. 2016 Aug;94:57-63 - https://www.ncbi.nlm.nih.gov/pubmed/?term=Three-year+Follow-up+Results+of+a+Prospective%2C+Multicenter+Study+in+Overactive+Bladder+Subjects+Treated+With+Sacral+Neuromodulation

- Siegel et al., Five-Year Follow-up Results of a Prospective, Multicenter Study in Overactive Bladder Subjects Treated with Sacral Neuromodulation, The Journal of Urology, Vol. 199, 1-8, (2017) - https://www.ncbi.nlm.nih.gov/pubmed/?term=Five-Year+Follow-up+Results+of+a+Prospective%2C+Multicenter+Study+in+Overactive+Bladder+Subjects+Treated+with+Sacral+Neuromodulation

- Van Kerrebroeck et al., Results of sacral neuromodulation therapy for urinary voiding dysfunction: outcomes of a prospective, worldwide clinical study - J Urol. 2007 Nov;178(5):2029-34 - https://www.ncbi.nlm.nih.gov/pubmed/18436258

- **UK NICE and NHS guidelines**

  - Clinical Commissioning Policy: Sacral Nerve Stimulation for Overactive Bladder - Reference: NHS England E10/P/b - https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/10/e10pb-sacrl-nrve-stimltn-bladdr.pdf

  - NICE CG97 - Lower Urinary Tract Syndrome in Men (2013) - https://www.nice.org.uk/guidance/cg97

  - NICE CG171 - Urinary incontinence in women: the management of urinary incontinence in women (2013) - https://www.nice.org.uk/guidance/cg171

  - NICE NG123 - Urinary incontinence and pelvic organ prolapse in women management (2019) - https://www.nice.org.uk/guidance/ng123 - https://www.nice.org.uk/guidance/ng123

  - NICE IPG64 - Sacral nerve stimulation for urge incontinence and urgency frequency (2004) - https://www.nice.org.uk/guidance/ipg64

  - NICE MIB164 - Axonics sacral neuromodulation system for overactive bladder and faecal incontinence (2018) - https://www.nice.org.uk/advice/mib164

- **Other references**

  - Cameron et al., Battery Explantation After Sacral Neuromodulation in the Medicare Population - Neurourology and Urodynamics 32:238–241 (2013) - https://www.ncbi.nlm.nih.gov/pubmed/?term=Battery+Explantation+After+Sacral+Neuromodulation+in+the+Medicare+Population

  - https://magnetic-resonance.org/ch/21-01.html

  - Lettieri et al., Clinical outcome of deep brain stimulation for dystonia: constant-current or constant-voltage stimulation? A non-randomized study - Eur J Neurol. 2015 Jun;22(6):919-26 - https://www.ncbi.nlm.nih.gov/pubmed/25041419

  - Lloyd et al., Removal of Sacral Nerve Stimulation Devices for Magnetic Resonance Imaging: What Happens Next? - Neuromodulation. 2017 Dec;20(8):836-840 - https://www.ncbi.nlm.nih.gov/pubmed/?term=Removal+of+Sacral+Nerve+Stimulation+Devices+for+Magnetic+Resonance+Imaging%3A+What+Happens+Next%3F

- Peters et al., Predictors of Reoperation After Sacral Neuromodulation: A Single Institution Evaluation of Over 400 Patients - Neurourology and Urodynamics 36:354–359 (2017) - https://www.ncbi.nlm.nih.gov/pubmed/?term=Removal+of+Sacral+Nerve+Stimulation+Devices+for+Magnetic+Resonance+Imaging%3A+What+Happens+Next%3F

10 Appendices

Appendix A: Search strategy for clinical evidence

Describe the process and methods used to identify and select the studies relevant to the technology. Include searches for published studies, abstracts and ongoing studies in separate tables as appropriate. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	July 31, 2019
Date span of search:	All publications until July 31, 2019

List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.

Objective

The objective of this systematic literature search is to present clinical evidence of the safety and effectiveness in using sacral neuromodulation systems for treating overactive bladder (OAB), urinary retention (UR) and fecal incontinence (FI).

Database

The scientific literature database *Entrez PubMed/Medline* will be used to perform a search of published investigational clinical data, namely data available for current state-of-the-art medical practices involving the use of the InterStim System.

The database has over 24 million citations and contains all Medline indexd articles which include results from other search engines such as: Google Scholar, MedSci Medical Journal Database, MedBioWorld, etc.

Methods

Search terms:

The following terms or combinations thereof were used during the literature search:

- Sacral
- nerve
- stimulation
- modulation
- neuromodulation
- neurostimulator
- rechargeable
- fecal
- incontinence
- urinary
- bowel
- retention
- bladder
- overactive
- urge

The above terms were combined with the following equivalent device trade/brand names and model numbers:

- Axonics
- InterStim
- Medtronic
- Model 3058
- Model 3023

The specific search term combinations used for conducting the literature search are listed in Table 1. The methods for conducting this literature review consist of applying the inclusion/exclusion criteria of each article, the treatment of duplicate articles or data sets and the analysis performed on relevant articles.

Known and unknown treatment modalities will be searched for by key words. The total search results, along with all of the exclusions applied, are summarized below in **Table 1**. A visual representation of the literature search process can be found below in **Error! Reference source not found.**.

Table 1: Literature search results

Search ID	Search Terms	PubMed (up to 31 July 2019)
1	Interstim sacral modulation [any field] [English + Humans]	5
2	Interstim neuromodulation [any field] [English + Humans]	78
3	Interstim Neurostimulator [any field] [English + Humans]	13
4	Medtronic sacral modulation [any field] [English + Humans]	4
5	Medtronic neuromodulation [any field] [English + Humans]	122
6	Medtronic neurostimulator [any field] [English + Humans]	26
7	Interstim urinary [any field] [English + Humans]	91
8	Interstim bowel [any field] [English + Humans]	14
9	Interstim incontinence [any field] [English + Humans]	77
10	Interstim model 3058 [any field] [English + Humans]	0
11	Interstim model 3023 [any field] [English + Humans]	0
12	Interstim urinary retention [any field] [English + Humans]	34
13	Interstim overactive bladder [any field] [English + Humans]	26
14	Interstim urinary urge [any field] [English + Humans]	33
15	Interstim fecal [any field] [English + Humans]	23
16	Interstim fecal incontinence [any field] [English + Humans]	23
17	Interstim bowel control [any field] [English + Humans]	2
18	Sacral Nerve stimulation fecal incontinence [any field] [English + Humans]	396
19	Sacral Nerve stimulation urinary incontinence [any field] [English + Humans]	312
20	Sacral neuromodulation fecal incontinence [any field] [English + Humans]	164
21	Sacral neuromodulation urinary incontinence [any field] [English + Humans]	290
22	Rechargeable AND sacral AND (neuromodulation OR stimulation OR neurostimulation)	14
	Subtotal of literature search results	**1747**
	Duplicates	801
	Unique results from literature search	946
	Exclusions applied (see details below)	937
	Articles included	9
	Additional Articles (latest follow-up.)	2
	Total Articles included from literature	**11**
	RELEVANT	**11**
	Exclusions applied**	
	Duplicate/Duplicate Data Set	801
	>15 yrs, non-RCT	1
	Animal data	3
	Case report/series	38
	Cost assessment	20
	Dissimilar device	161
	Dissimilar disease state	17

	Dissimilar indication	77
	Dissimilar medical area	7
	Dissimilar patient population	64
	Dissimilar technique	1
	Intra-device comparison	2
	Latest article included	1
	N<100, >15yrs	83
	N<100, non-RCT	42
	No abstract	53
	No author	4
	No clinical data/outcome	105
	No device evaluation/no device identification	32
	Patient care management/clinical practice	6
	Patient physiology/anatomy	30
	Study type	124
	Technical note/clinical technique	66

*Database search contains the following limiters: “human study subjects”, “English language”, “clinical trials”.

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

Enter text.

Inclusion and exclusion criteria:

Based on the known quality of study documentation, the search for scientific publications will be limited to original research articles on clinical trials. Study methods will be limited based on the labelled indications for use of the device. Since English is the primary language of the evaluators, only English articles will be included from the search results to ensure the evaluators are able to adequately interpret the data. Additional exclusion criteria have been applied to reduce the possibility of inadequate and/or substandard study data inclusion as noted below.

Inclusion Criteria

- Articles where study subject population is overactive bladder (OAB), including urinary incontinence, urgency urinary incontinence and urinary frequency
- Human randomized controlled clinical trials
- Peer-reviewed journal publications, or equivalent
- Methods section clearly indicates that the InterStim System was the subject of the study
- Follow-up outcome data included evaluations of mortality, morbidity and/or clinical success

Exclusion Criteria

- Articles where study subject population has pre-dominantly stress incontinence
- Articles >15 years old
- Studies with N < 100 (non-randomized; greater than 15 yr; except for Sponsor studies)
- Dissimilar patient populations (e.g. pediatric, first-treatment, Asian-only populations, etc.)
- Duplicate publications (e.g. identical individual citations and/or identical citations within meta-analysis/systematic review included for review)
- No long-term follow-up data for safety / efficacy
- Dissimilar device (e.g. tibial nerve stimulation, spinal cord stimulation)
- Animal trials (small or large); Case Reports
- Retrospective case series ; Review or meta-analysis articles
- Technical notes ; Bench/anatomical model reports
- Book chapters, abstracts, scientific presentations, single case reports, white papers and other monographs not published in peer-reviewed journals
- Random experience and reports lacking sufficient detail to permit scientific evaluation
- Unsubstantiated opinions and lack of statistical design (patient population does not support statistical significance)
- Medicinal substance focus as patient population is refractory (resistant to medication)
- Foreign language only articles (not available in English)
- Studies of clinician specific technique(s) not reflecting state of the art
- Study focus on disease state evaluation (e.g. progression of healthy eyes, physiological/anatomical states, etc.)
- Intra-device comparative studies
- Studies with publication dates outside specified limits

• Technical studies, or those where non-standard SNM parameters were used or where other forms of sacral neuromodulation (e.g. transcutaneous) are employed • Indications outside those of the Axonics SNM System (e.g. non-chronic fecal incontinence, obstructive urinary retention, FI secondary to organic pathologies) • Lack of information on elementary aspects (author, study methods, number of patients, adverse events, clinical outcomes) • Conclusions not aligned with study results • Illegal activities
Data abstraction strategy:

Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

Duplicate Articles and Data Sets

This literature review will exclude any duplicate articles found in the search results. Duplicate articles are identified by checking the results for duplicate PMIDs (PMID is the unique ID assigned to each article found on PubMed).

This review will also consider whether duplicate data sets between studies are present. Where identical data sets and outcomes are present, the evaluator will manually eliminate duplicates ensuring only a single data source is used for review. If the patient population is identical (or reasonably so) but the study data, endpoints and/or outcomes differ, then both data sources will be included in the assessment.

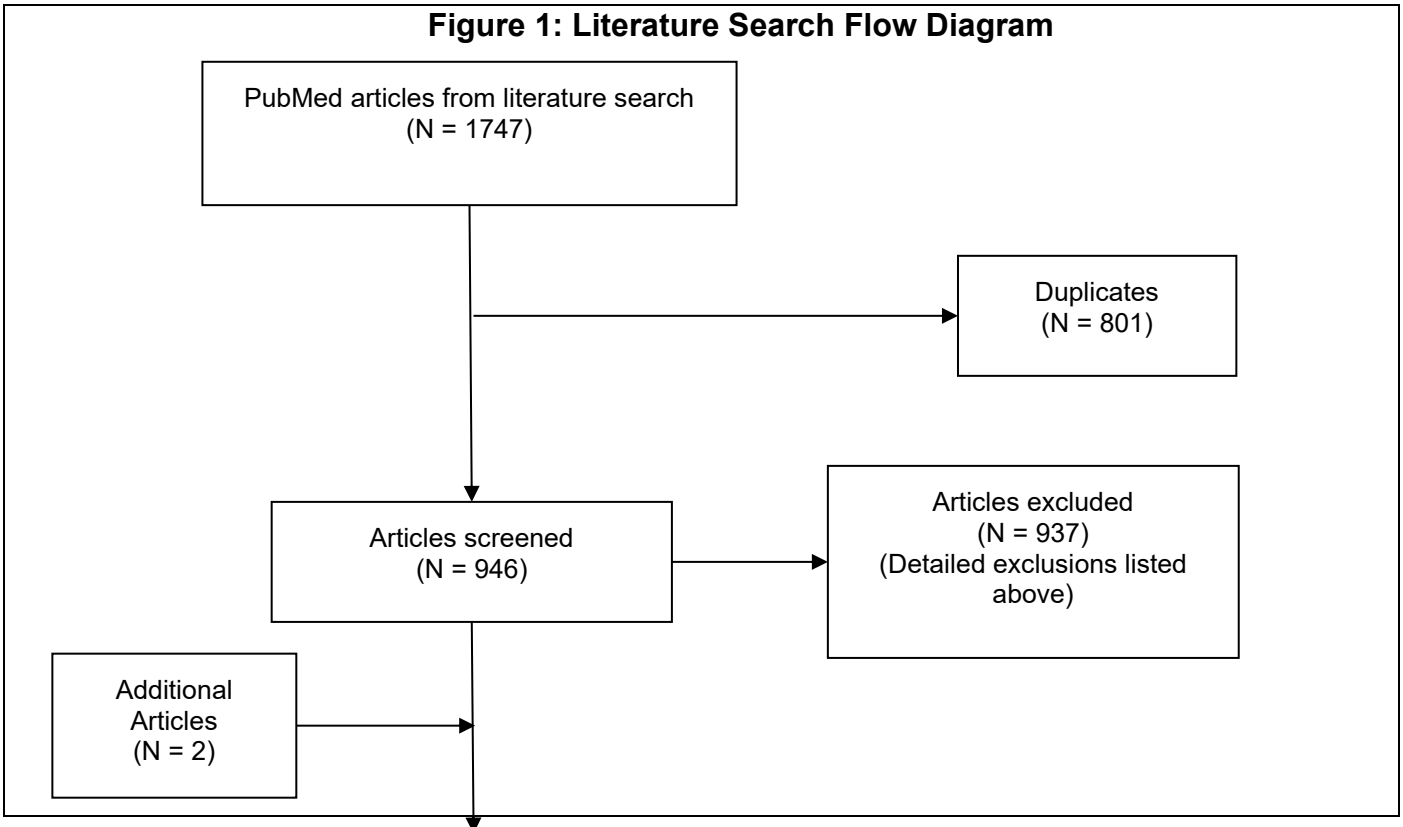
Analysis

All relevant search results will be included. These results will be analyzed for the following:

- Effectiveness
- Safety including intraoperative, short-term and long-term effects.

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

Figure 1: Literature Search Flow Diagram



Results: A total of 11 published articles are used for the clinical evaluation.

Structured abstracts for unpublished studies

Study title and authors
Introduction
Objectives
Methods
Results
Conclusion
Article status and expected publication: Provide details of journal and anticipated publication date

Appendix B: Search strategy for adverse events

Date search conducted:	Enter text.
Date span of search:	Enter text.
List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	
Enter text.	
Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):	
Enter text.	
Inclusion and exclusion criteria:	
Enter text.	
Data abstraction strategy:	
Enter text.	

Adverse events evidence

List any relevant studies below. If appropriate, further details on relevant evidence can be added to the adverse events section.

Study	Design and intervention(s)	Details of adverse events	Company comments
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text

Text	Text	Text	Text

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

Enter text.

Appendix C: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No	☐	If no, please proceed to declaration (below)
Yes	X	If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information provided in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
#19	X Commercial in confidence ☐ Academic in confidence	Commercial in confidence – sensitive financial information.	No limit in time – indefinite confidentiality.
Details	Axonics prefers not to publicly share information regarding the volume of implants performed at hospitals using the Axonics SNM System in the UK as this information is not publicly disclosed to investors		
#53	X Commercial in confidence ☐ Academic in confidence	Commercial in confidence – sensitive research and development data.	
Details	Testing methodology and results are central in Axonics' research and development strategy, and therefore constitute sensitive information. The Axonics Neurostimulator's 15+ years longevity claim has been approved by both its CE Mark in Europe (BSI), its Health Canada License, its TGA Approval in Australia, its FDA PMA Approval in the US and appears on the product labelling in all these geographies. Therefore, testing details provided in this application are a courtesy of Axonics, with the aim to explain to NICE how the claim for 15+ years longevity was approved. Given this information is sensitive and only supports an already approved claim, Axonics would like it to remain confidential.		No limit

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*		**Date:**	September 9, 2019
Print:	Karen L. Noblett, M.D.	**Role / organisation:**	Chief Medical Officer, Axonics Modulation Technologies
Contact email:	knoblett@axonics.com		

Appendix D: List of attachments

- CE Mark certificates
- ISO certificate 13485
- Declaration of Conformity
- Blok et al., Three month clinical results with a rechargeable sacral neuromodulation system for the treatment of overactive bladder – Neurourol.Urodyn. 2018 Feb;37(S2):S9-S16
- Blok et al., Programming settings and recharge interval in a prospective study of a rechargeable sacral neuromodulation system for the treatment of overactive bladder – Neurourol.Urodyn. 2018 Feb;37(S2):S17-S22
- OAB full care pathway diagram from CG171
- Lane et al., Treatment of urinary urgency incontinence with the Axonics® miniaturized, rechargeable SNM system: Clinical outcomes of the ARTISAN-SNM pivotal study - AUGS 2019 presentation + certification of data from primary author Dr Lane
- Blok et al., Two years outcomes of the treatment of overactive bladder with a rechargeable SNM System - unpublished manuscript
- Lane et al., One-year outcomes of the Axonics® System for treatment of urinary urgency incontinence – SUFU 2020 abstract

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

MT417 Axonics sacral neuromodulation system for overactive bladder

Company evidence submission

Part 2: Economic evidence

Company name	**Axonics Modulation Technologies, Inc.**
Submission date	October 2, 2019
Contains confidential information	Yes

Contents

1 Published and unpublished economic evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		19
Number of studies identified as being relevant to the decision problem.		19
Of the relevant studies identified:	Number of published studies.	19
	Number of abstracts.	n.a.*
	Number of ongoing studies.	n.a.*

* abstracts and ongoing studies were only identified for the clinical evidence

List of relevant studies

In table 1, provide brief details of any published or unpublished economic studies or abstracts identified as being relevant to the decision problem.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data provided.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

Table 1 Summary of all relevant studies (published and unpublished)

Note:

Our search criteria, and inclusions/exclusions as listed in the appendix, were intentionally designed to include all economic studies of sacral nerve stimulation for overactive bladder. The reason was that we wanted to provide all evidence of SNM economics for the treatment of overactive bladder. If we were to have the search defined more strictly and would have limited to the scope narrowly to only identify studies that assess rechargeable vs. non-rechargeable, information that might be relevant to the committee would not have been identified.

It was therefore expected that the majority of studies would ultimately be labelled as 'not relevant' for the strict decision considered in our economic model.

Data source	Author, year and location	Patient population and setting	Intervention and comparator	Unit costs	Outcomes and results	Sensitivity analysis and conclusion
Cost-Effectiveness of Sacral Neuromodulation Compared to Botulinum Neurotoxin A or Continued Medical Management in Refractory Overactive Bladder	Arlandis et al. 2011, Spain	Refractory incontinent idiopathic overactive bladder patients in the Spanish healthcare system	Intervention: sacral neuromodulation (SNM) Comparators: Botulinum neurotoxin A (BoNT-A) or continued optimized medical treatment (OMT).	**Cost Inputs:** **Pre-Procedure costs:** SNM test: 558€ SNM: 102€ BoNT-A: 572€ OMT: - Cystoplasty: 736€ **Procedure and drug costs:** SNM test: 2781€ SNM: 9734€ BoNT-A: 1192€ OMT: First-line drug cost: 153€ Second-line drug cost: 189€ Third-line drug cost: 20€ Fourth-line drug cost: 51€ Cystoplasty: 2783€ **Adverse Event costs (per annum)** SNM test: - SNM: 436€ BoNT-A: 132€ OMT: 302€ Cystoplasty: 415€	"[…] at 10 years, the cumulative costs of SNM, BoNT-A, and OMT were €29,166, €29,458, and €29,370, respectively, with cumulative QALYs of 6.89, 6.38, and 5.12." "[…ICERs] for SNM demonstrate that although the initial costs for SNM are higher than those for the other treatments, decreasing follow-up costs coupled with consistently greater effectiveness in the long term make SNM the economically dominant option at 10 years." The budget impact analysis showed an increment of 0.2% to 1.25% in total costs and is considered to be small in Spain in the evaluated 4 years.	Applied different parameters in the DSA "demonstrate the robustness of the inputs, obtaining similar results of dominance at 10 years and cost effectiveness at 5- and 7-year time frames." Probabilistic sensitivity analysis was adapted and showed "[…] that 99.7% and 99.9% (for SNM vs. BoNT-A and OMT, respectively) of the 1000 Monte Carlo iterations fall within the €30,000 cost-effectiveness threshold, considered to be acceptable in Spain." "[…] SNM provides a considerable possibility of symptom and quality-of-life improvement and is

				Follow-Up-Costs Up to first 3 months: SNM test: 94€ SNM: 166€ BoNT-A: 500€ OMT: 707€ Cystoplasty: 4249€ After first 3 months: SNM test: - SNM: 98€ BoNT-A: 233€ OMT: 707€ Cystoplasty: 415€ Follow-up after treatment failure: SNM test: 867€ SNM: 937€ BoNT-A: 1554€ OMT: 732€ Cystoplasty: 8536€		cost-effective compared to BoNT-A or continued OMT."
Sacral neuromodulation and Botulinum toxin A for refractory idiopathic overactive bladder: a cost-utility analysis in the perspective of	Bertapelle et al. 2015, Italy	Refractory incontinent idiopathic overactive bladder (OAB) patients in the Italian Healthcare System	Intervention: Sacral Neuromodulation (SNM) Comparator: Botulinum neurotoxin A (BoNT-A)	**Cost-Inputs:** **SNM-cost**: SNM test—pre-procedure costs (€):213,65 SNM test—cost (including implanted devices) (€) 5,622.35	„[…] at year ten: cumulative costs were €32,975 for early SNM and €33,309 for early BTXA, while cumulative QALYs were 7.52 and 6.93, respectively." Subsequently the	"At year ten, [deterministic sensitivity analysis] suggests the results robustness and 99.8 % of the PSA iterations fell within

Italian Healthcare System (INHS)				SNM IPG implantation—pre-procedure costs (€): 104.59 SNM IPG implantation—cost (including implanted devices) (€): 9,433.34 **SNM adverse event cost:** Lead repositioning for migration or decreased clinical response—cost (including implanted devices) (€):5,873.03 Lead replacement for breaking—cost (including implanted devices) (€):5,684.37 Generator repositioning (for pain, infection, other)—cost (€): 2,674.69 Lead explantation—cost (€):724.55 **BoNT/A-cost:** BoNT/A pre-procedure costs (€): 217,07 BoNT/A injection cost (including 100U,	ICUR showed dominance of the SNM strategy. Additionally,“ […] SNM appears to be cost effective (i.e. under €40.000/QALY) from year three (€21,259/QALY) onwards […]”	the cost-effectiveness threshold.“ “A therapeutic strategy starting with SNM may be considered cost effective in the midterm and cost saving in the long-term treatment of idiopathic OAB from the INHS perspective.”

				onabotulinumtoxin A) (€): 1,654.99 **BoNT/A adverse events cost:** Urinary tract infections—cost (€): 71.65 PVR-related catheterisation—cost (€): 153.61		
Real world performance of SNM and onabotulinumtoxinA for OAB: Focus on safety and cost	Chughtai et al. (unpublished - Accepted: 17 July 2019), New York state	Patient population: 2,680 OAB patients were included in total with 1,328 who underwent SNM and 1,352 who had onabotulinumtoxinA. "Average age was 61.7 with a standard deviation of 16.3 and 82.7% were females. Setting: New York states surgical register {Statewide Planning and Research Cooperative System (SPARCS)}	Intervention: Sacral Neuromodulation (SNM) Comparator: onabotulinumtoxinA	No unit costs presented	Cost-comparison results: After propensity score matching and three years the total costs of onabotulinumtoxinA were lower ($3,454) compared to SNM-therapy ($16,189). Similar results were found before matching. Costs increased only slightly from 1-year total cost to 3-year total cost. Safety comparison results: Within three-years, 26.1% SNM patients experienced re-interventions (i.e. removal, revision, replacement). In the onabotulinumtoxinA group, 41.2% of the patients received	Sensitivity analysis was not applicable. "SNM implantation was more expensive compared to onabotulinumtoxinA injection; however, SNM patients had lower rate of complications when compared to onabotulinumtoxinA patients."

					another onabotulinumtoxinA. "After propensity score matching, onabotulinumtoxinA patients had a higher risk of 30-day complications including urinary tract infection (RR: 3.60 [1.34-9.70], p<0.01), hematuria (RR: 5.00 [1.71-14.63], P<0.01), urinary retention (RR: 3.25 [1.06-9.97], P=0.03) and had a higher risk of ER visit (RR: 1.67 [1.22-2.30], P<0.01) during 30 days when compared to SNM use."	
OnabotulinumtoxinA in the treatment of overactive bladder: a cost-effectiveness analysis versus best supportive care in England and Wales	Freemantle et al (2016), England and Wales	Adult patients with idiopathic overactive bladder, not adequately managed with anticholinergics, in the national healthcare systems of England and Wales	Intervention: OnabotulinumtoxinA (BOTOX®) + best supportive care (BSC) Comparator: BSC alone	**Cost-Inputs:** OnabotulinumtoxinA (100 U vial): £138.20 Anticholinergics (per patient per month): £28.31 Antibiotics (per course): £0.59 Incontinence pads (per pad): £0.25 Catheters for CIC (per catheter): £0.75	"The total discounted cost per patient over the 10-year period was £10,160 with onabotulinumtoxinA and £11,572 with BSC. Total QALYs were 6.908 with onabotulinumtoxinA and 6.695 with BSC." The ICER showed dominance in all but two scenarios. However, in both	The results of the model showed robustness in a one-way sensitivity analysis after changing individual parameters. "OnabotulinumtoxinA remained dominant over BSC in all but two scenarios tested; it was also economically

				OnabotulinumtoxinA administration: £219.00 Specialist physician visit: £102.00 Physician visit to treat UTI: £63.00 Removal of temporary SNS electrodes: £1166.00 PNE test (one-stage test): £1485.00 One-stage SNS implant (electrode and modulator implants): £8641.00 SNS device explant: £923.00 SNS surgical revision: £592.00 SNS battery replacement: £6623.00 SNS follow-up physician visit: £319.00	cases OnabotulinumtoxinA was cost-effective.	dominant when compared directly with SNS therapy." "When uncertainty was taken into account via a probabilistic sensitivity analysis, there was an 89 % probability that the ICER was below £20,000 […]." "In conclusion, onabotulinumtoxinA appears to be a cost-effective treatment for overactive bladder compared with BSC alone."
Economic evaluation of sacral neuromodulation in overactive bladder: A Canadian perspective	Hassouna and Sadri (2015), Canada	Idiopathic overactive bladder (OAB) patients in the Canadian provincial health system	Intervention: Sacral-neuromodulation (SNM) Comparator: Botulinum-toxin (BonT-A) or	**Cost-Inputs:** **Only methods without actual unit costs could be extracted:** „Healthcare resource utilization and associated direct	"The annual incremental cost of SNM vs. BonT-A was $7237 in year 1 and -$9402 in year 10 and was between $8878 and -$11 447 vs. OMT."	"In the base-case deterministic analysis, the ICER for SNM vs. BonT-A and OMT were within the acceptable range ($44 837 and $15 130, respectively) at the second year of

			optimized medical treatment (OMT).	medical costs from a Canadian provincial healthcare system were used in the model. The sources of healthcare resources used included: procedure, medications, complications, staff, diagnostics, disposables, devices, and follow-ups."	"The annual (year 1–10) incremental quality-adjusted life years for SNM vs. BonT-A was 0.05 to 0.51 and SNM vs. OMT was 0.19 to 1.76." "[…] the corresponding ICER shows dominance in all ranges from the 5- to 10-year period"	therapy, and SNM was dominant in consequent years. In the base-case analysis the probability of ICER being below the acceptability curve (willingness-to-pay $50 000) was >99% for SNM vs. BonT-A at year 3 and >95% for OMT at year 2." "SNM is a cost-effective treatment option to manage patients with refractory OAB when compared to either BonT-A or OMT. From a Canadian payers' perspective, SNM may be considered a first-line treatment option in management of patients with OAB with superior long-term outcomes."
Cost-Effectiveness of Test Phase Implantation Strategies for InterStim® Sacral Neuromodulation	Kantartzis and Shepherd, 2013, USA	Patients with refractory overactive bladder in the US Medicare health insurance program	Cost-effectiveness model of six possible options for treatment of refractory urgency:	**Cost-Inputs:** Chronic urinary incontinence: $5424 PNE: $976	Reported total cost and total QALYs over the 54-month modelling cycle were:	"Sensitivity analysis generated an acceptability curve outlining the most cost-effective strategy at various

			1. Unilateral placement using PNE 2. Bilateral placement using PNE 3. Unilateral stage I placement of permanent electrode leads 4. Bilateral stage I placement of permanent electrode leads 5. Combined stage I and II placement with no testing phase 6. No InterStim® treatment	Stage I, unilateral: $6917 Stage I, bilateral: $10,371 Stage II: $15,100 Combined stage I/II: $22,017 InterStim® revision (leads only): $1648 InterStim® removal (IPG and leads): $2969	No InterStim® treatment: $24,409 and 3.420 QALYs Unilateral placement using PNE: $26,948 and 4.036 QALYs Unilateral stage I placement of permanent electrode leads: $27,169 and 4.201 QALYs Bilateral stage I placement of permanent electrode leads: $28,081 and 4.321 QALYs Bilateral placement using PNE: $28,136 and 4.104 QALYs Combined stage I and II placement with no testing phase: $31,824 and 4.113 QALYs "Bilateral PNE and combined stage I/II were excluded from cost-effectiveness calculations by simple dominance as there were options which were more effective and less expensive than both of these. Unilateral PNE was excluded by extended	WTP thresholds […]. This curve confirmed that bilateral stage I was the most likely cost-effective option for all WTP thresholds greater than $6000 per QALY." „Bilateral and unilateral stage I lead placement were the only cost-effective strategies. Bilateral stage I was preferred due to greater effectiveness."

					dominance. Both unilateral stage I and bilateral stage I were cost-effective options with ICERs of $3533 and $7600, respectively."	
Cost-effectiveness analysis of sacral neuromodulation and botulinum toxin A treatment for patients with idiopathic overactive bladder	Leong et al. 2010, Netherlands	Patients with idiopathic overactive bladder in the Dutch health care system	Intervention: Sacral neuromodulation (SNM) Comparator: botulinum toxin A (BTX)	**Cost Inputs:** SNM pre-procedure costs: €278 First-stage tined lead procedure (including material) costs: €3.445 Second-stage tined lead procedure (including Interstim 1) costs: €9.150 SNM surgical revision costs: €2.590 SNM surgical removal/replacement costs when infected: €11.448 BTX pre-procedure costs: €290 BTX procedure (including 200 U of BTX) costs: €1.564 Urinary retention costs: €449 UTI costs: €100 Outpatient follow-up costs: €70	The official base case analysis was at year 5, however at this point the longest available time period is presented. At year ten, the cumulative costs were €36,878 for SNM therapy and €31,485 for BTX therapy, while cumulative QALYs were 8.69 and 8.32, respectively. This results in an ICER of €14.493 per QALY.	One-way sensitivity analysis and a second-order Monte Carlo simulation were assessed to show robustness of the model. "Sensitivity analyses showed that over a 5-year time horizon the ICER remained below the €40.000 threshold for cost-effectiveness when SNM was performed under local anaesthesia whereas BTX was not, when the drop-out rate was changed to 2% or 6% and when the utility for incontinence or no improvement was changed to 0.80 […]. SNM was not cost-effective (ICER > €40 000) in all other scenarios, such as when BTX was

				Pads costs: €0.45		conducted under local anaesthesia or when PNE or bilateral testing was used for SNM […].“ “Starting with SNM, treatment is cost-effective after 5 years compared to BTX. However, in some scenarios, such as the use of local anaesthesia for BTX treatment and SNM peripheral nerve evaluation or bilateral test, SNM was not cost-effective.”
Outcome and Cost Analysis of Sacral Nerve Modulation for Treating Urinary and/or Fecal Incontinence	Leroi et al. 2011, France	190 patients with urinary incontinence alone (out of 369 patients in total – faecal incontinence and double incontinence {faecal and urinary} excluded for the purpose of the submission) attended this prospective, multicentre cohort study. Costs were estimated from the	Intervention: Sacral nerve Modulation (implanted group) Comparator: Non-SNM (therapeutic alternatives such as: continued conservative treatment or augmentation enterocystoplasty, urinary diversion, or bladder wall	**Cost Inputs:** (Faecal incontinence costs excluded) *Temporary test stimulation* Material (including device): With temporary electrode (stage II): €223.7 With definitive electrode (stage I): €694.2 Operation	“The median overall cost per patient in the first 2 years after the SNM treatment was € 16,403 (mean: €16,310) [n=78] for patients implanted for urge urinary incontinence […]” “The adjusted cost analysis revealed that treating urge urinary incontinence with SNM costed an average of € 8525	“Using a more than 50% improvement in urge urinary continence as the effectiveness unit, ICER was estimated at €94,204 per patient at the 24-month follow-up.” In addition, SNM had an ICER of €110,741 per QALY gained. The SNM is a cost-effective treatment for urge urinary

		French national health system perspective.	injection with botulinum toxin.)	With temporary electrode (stage II): €109.8 With definitive electrode (stage I): €179.9 Extra costs for hospital stays Urinary incontinence: Day case: €678 Inpatients: €3598.6 *Implantation* Material (including device) Stage I: €5385 Stage II: €5385 Operation: €179.9 Extra costs for hospital stay Urinary incontinence: €3598.6 *Follow-up* Consultations: €25 Stimulator settings: €52.1 *Complications* Lead migration: €179.9 Explantation: €44.4	more per participant the first 2 years (95% CI, € 6,686–€ 10,364) than alternative treatments (P = 0.001).” The SF-36 Quality-of-Life assessment in urge UI patients (implanted vs non-implanted) at 24 months resulted in: Physical functioning: 75 vs 60 Role physical: 50 vs 50 Bodily pain: 51 vs 51 General Health: 52 vs 43,5 Vitality: 45 vs 42.5 Social functioning: 63 vs 50 Role emotional: 100 vs 83,5 Mental health: 56 vs 48 Physical component summary: 44 vs 39	and/or faecal incontinence.

					Mental component summary: 44 vs 39	
Cost of Neuromodulation Therapies for Overactive Bladder: Percutaneous Tibial Nerve Stimulation Versus Sacral Nerve Stimulation	Martinson, MacDiarmid and Black et al. 2013, USA	Patients with refractory overactive bladder in the US Medicare program	Intervention: Percutaneous tibial nerve stimulation Comparator: Sacral nerve stimulation	**Cost Inputs:** Physician for 1 session of PTNS 12-wk trial: $129 Physician for 1 evaluation and management visit for PTNS therapy: $75 Physician for PTNS continuous therapy/wk: $129 {Av to facility for PTNS AE (Included in physician payment): $0} Av to physician for PNTS AE: $69 Physician for SNS continuous therapy: $83 To hospital for SNS explant: $2,476 To physician for SNS explant: $195 To hospital or facility for inpt. SNS implant: $9,202 To hospital or facility for outpt. SNS implant: $20,837	”Costs differed markedly after SNS implantation with costs per patient […] more than 3 times higher at 2 years ($14,160 for SNS vs $3,850 for PTNS). “Effectiveness was measured as the percent of patients still on therapy at a given time.” “At 2 years 48% of patients continued on PTNS compared to 49% on SNS.” ICER: “In the base case the cost per additional patient treated with SNS was approximately $537,000 during 2 years.”	“Sensitivity analyses revealed that under a wide range of conditions PTNS remained significantly less costly than SNS.“ “This study demonstrates that PTNS is a cost-effective way to deliver neuromodulation treatment for patients with OAB refractory to conservative and drug therapy.”

				To physician for SNS implant: $799 Paid to hospital or ambulatory surgical centre for outpt SNS test: $1,901 Paid to physician for SNS test at hospital: $623 Paid to physician for SNS test in office: $1,464 To hospital for outpt SNS revision: $2,476 To physician for SNS revision: $195		
Cost-effectiveness of overactive bladder treatments: from the US payer perspective	Murray et al. 2019, USA	Refractory OAB patients in the US health care system	Interventions: onabotulinumtoxinA (onabotA), implantable sacral nerve stimulation devices (SNS), percutaneous tibial nerve stimulation (PTNS), anticholinergic medications and mirabegron Comparator: Best supportive care (BSC)	**Cost Inputs:** **Costs and resource use of onabotA:** Per injection unit cost of onabotA 100U: $591 Administration as hospital outpatient: $581 Administration in ambulatory clinic office/physician office: $311 Administration in ambulatory surgery centre: $1605	At 10 years the total costs were: BSC: $11,460 OnabotA 100U: $15,049 SNS: $27,823 PTNS: $14,103 Mirabegron (25mg): $14,745 Mirabegron (50mg): $14,738 Tolterodine ER (4 mg): $12,776 Solifenacin (5mg): $13,342 Solifenacin (10mg):	"Sensitivity analyses, both one-way and probabilistic, supported the base-case findings." "Model results were shown to be robust, with only a minor impact on the onabotA ICER based on the varying assumptions assessed in sensitivity and scenario analyses."

			The Model design "was a collection of two-arm models with BSC as the reference treatment".	**Cost (and resource use) for BSC** Average monthly cost of anticholinergics: $211 **Cost and resource use for SNS** Cost of testing: $11,080 Cost of the permanent implant: $16,336 Cost of additional physician visits (follow-up): $220 Cost of battery replacement: $16,336 Cost of revision: $1091 Cost of device explantation: $16,336 **Cost and resource use for PTNS** Cost of treatment (0–3 months): $1483 Cost of treatment (3–6 months): $618	$13,335 Total number of QALYs gained at 10-years were: BSC: 7.069 OnabotA 100U: 7.179 SNS: 7.125 PTNS: 7.106 Mirabegron (25mg): 7.073 Mirabegron (50mg): 7.073 Tolterodine ER (4 mg): 7.071 Solifenacin (5mg): 7.072 Solifenacin (10mg): 7.073 Estimated ICER ($ per QALY) BSC: N/A OnabotA 100U: $32,680 SNS: $288,096 PTNS: $71,126 Mirabegron (25mg): $794,395 Mirabegron (50mg): $697,803	"PSAs showed that onabotA is the most cost-effective treatment and that there is close to 100% probability that the ICER for onabotA is <$50,000 per QALY gained." "Compared with BSC, onabotA 100U was the most cost-effective treatment option for patients with refractory OAB."

				Cost of treatment (after 6 months): $371 **Cost and resource use for mirabegron and anticholinergics** Mirabegron 25 and 50 mg: $282 Tolterodine ER: $208 Solifenacin 5 and 10 mg: $274 **Adverse event (resource use and) cost**: Cost per CIC: $3 Medication cost to treat UTI: $4 Medical care cost to treat UTI: $73	Tolterodine ER (4 mg): $687,849 Solifenacin (5mg): $527,018 Solifenacin (10mg): $409,245	
Comparison of patients undergoing a two-stage sacral nerve stimulation procedure: is there a cost benefit for a single-stage procedure?	Nikolavsky et al. 2011, USA	145 (14 needed explantation) Patients undergoing SNS in a hospital setting in the U.S.	Cost Analysis between single-stage and two-stage sacral nerve stimulation	**Reimbursement by BC/BS and Medicare (implantation costs only):** Stage 1 reimbursements - Medicare: Hospital fees: $5,729.3 Anaesthesia costs: $780	"Total Medicare and Blue Cross/Blue Shield (BCBS) reimbursement for a two-stage procedure was calculated at $21,428/case and $26,968. Implanting the lead and generator as a single-stage would cost Medicare and BCBS $20,696 and $21,602, respectively. Since	No sensitivity analysis was applicable. "Performing SNS as a single-stage procedure would result in a cost savings and benefit patients by significantly reducing the patient's operative and

				Surgeon fees: $966.6 Stage 1 reimbursements – BC/BS: Hospital fees: $8,567.7 Anaesthesia costs: $780 Surgeon fees: $1,149.9 Stage 2 reimbursements - Medicare: Hospital fees: $13,124.0 Anaesthesia costs: $540 Surgeon fees: $288.8 Stage 2 reimbursements – BC/BS: Hospital fees: $15,560.7 Anaesthesia costs: $540 Surgeon fees: $370.0 Single-stage reimbursements – Medicare: Hospital fees: $18,859.3	9.7% were explanted, overall cost saving might be significant: a single-stage approach would yield savings of $3,655/case (BC/BS) over a two-stage approach (after the cost of explantation is factored in).“	anaesthesia risks, discomfort, time lost from work, and burden on doctors, nurses, and staff.“

				Anaesthesia costs: $780 Surgeon fees: $1,056.7 Single-stage reimbursements – BC/BS: Hospital fees: $19,554.7 Anaesthesia costs: $780 Surgeon fees: $1,268.1		
Cost Profiles and Budget Impact of Rechargeable Versus Non-Rechargeable Sacral Neuromodulation Devices in the Treatment of Overactive Bladder Syndrome	Noblett et al. 2017, USA	OAB patients in the US healthcare system (payer perspective)	Intervention: Rechargeable SNM device Comparator: Non-rechargeable SNM Device	**Cost Inputs:** Implantation of whole system, outpatient (lead and neurostimulator): $17,947 Implantation of whole system, inpatient (lead and neurostimulator): $14,120 Implantation or replacement of neurostimulator, outpatient: $17,265 Implantation or replacement of neurostimulator, inpatient: $16,698	"At base-case assumptions, discounted 15-year costs for the non-rechargeable and rechargeable strategies were $64,111 and $36,990, respectively, resulting in total cost savings for the rechargeable strategy of $27,121 […]." Budget-Impact-Analysis: "Over the 15-year horizon, the gradual adoption scenario yielded potential discounted savings of $7.989 billion."	"These cost savings were found to be robust across a wide range of scenarios. Longer analysis horizon, younger patient age, and longer rechargeable neurostimulator lifetime were associated with increased cost savings." "Our findings suggest that, at current reimbursement rates, rechargeable neurostimulator device technology for sacral

				Removal without replacement, outpatient: $2,406 Removal without replacement, inpatient: $12,768 Outpatient programming, complex: $184 Lead revision (also applicable for lead fracture): $2,276 Cost of IV antibiotic treatment (4 weeks): $3,363		neuromodulation may deliver significant cost savings to payers over the course of treatment."
Sacral Nerve Stimulation for Urinary Urge Incontinence, Urgency-Frequency, Urinary Retention, and Fecal Incontinence	Medical Advisory Secretariat (Ontario Health Technology Assessment), 2005, Canada	Patients with urge incontinence in Ontario (estimation)	Cost analysis of SNS No comparator	**Cost Inputs (CAD):** Hospitalization Costs: $2,823 Device Costs: appr.: $10.000 – $14.000 Physician costs summed up in: total professional medical fees per case (expected): $1,439	"Total costs in the Ontario-Based Economic Analysis determined that total costs were approximately $2,823 for Hospitalization Costs + $10,000 to $14,000 for Device Costs + $1,439 for OHIP physician costs."	No sensitivity analysis was performed.
Comparative effectiveness of one versus two-stage sacral neurostimulation device placement	Patel et al. 2019, USA	OAB Patients receiving SNS in the US healthcare system (outpatient).	Intervention: One-stage SNS placement Comparator: Two-stage SNS placement	**Cost Inputs:** **(Medicare national average)** Incision for implantation of neurostimulator electrode array; sacral nerve	In a two-stage placement total initial procedure costs resulted in $6,170. Patients who had a successful conversion, the total cost was $18,474, if the conversion was	No sensitivity analysis was performed. "Our analysis of Medicare reimbursements rates for hospital

				(transforaminal placement): $6056 Fluoroscopy, up to one hour: $114 Insertion or replacement of peripheral or gastric neurostimulator pulse generator or receiver, direct or inductive coupling: $18,369 Electronic analysis of implanted pulse generator system: $105 Revision or removal of peripheral neurostimulator electrode array: $2,879 Revision or removal of peripheral or gastric neurostimulator pulse generator or receiver: $2,879	unsuccessful total cost was $2,879. In a one-stage placement total initial procedure costs resulted in $18,483. If patients had a successful conversion, no additional costs were assumed, if the conversion was unsuccessful total cost was $5,758.	outpatient SNS placement show that the cost effectiveness between a standard two-stage operative placement of the device to a one-stage placement of the device varies based on the rate of successful conversion and failure from the testing phase to the implantation phase. Our results suggest that in patients and providers with a successful conversion rate greater than 71%, placement of an SNS device in a one-stage procedure would be cost effective. Although this would result in a percentage of patients requiring a second more extensive procedure for generator and lead removal, a large percentage of patients in this circumstance would

						entirely avoid the risks and costs associated with a second procedure."
Cost-Effectiveness of Sacral Neuromodulation Versus Intravesical Botulinum A Toxin for Treatment of Refractory Urge Incontinence	Siddiqui et al. 2009, USA	Patients with refractory urge incontinence in the US (societal perspective)	Intervention: Sacral neuromodulation Comparator: Intravesical Botulinum A Toxin	**Cost Inputs:** Cost of botulinum injection: $1,690 Cost of SNS 1st stage lead placement: $5,720 Cost of SNS 2nd stage generator placement: $11,280 Cost of office management of SNS complication: $220 Cost of SNS surgical revision: $4,400 Cost of SNS removal: $1,195 Cost of urinary retention: $190 Cost of UTI: $85 Cost of persistent incontinence/3 mos: $180	"In the base case scenario sacral nerve stimulation was more expensive ($15,743 vs $4,392) and more effective (1.73 vs 1.63 quality adjusted life-years) than botulinum toxin A during a 2-year period. The incremental cost-effectiveness ratio was $116,427 per quality adjusted life-year."	"Our results did not change in sensitivity analyses despite varying costs, rates of efficacy and rates of adverse events through the range of reported values." "During a 2-year period botulinum toxin A was cost-effective compared to sacral neuromodulation for the treatment of refractory urge incontinence."
To stage or not to stage? — A cost minimization analysis of sacral neuromodulation placement strategies	Sun et al. 2019, USA	Patients with OAB in ambulatory surgery centres (ASC) and outpatient hospital departments (OHD) in the US	Intervention: Single-stage SNM placement Comparator: Two-stage SNM placement	**Cost Inputs:** **Physician fee** Stage-1 SNM placement: $687 Stage-2 SNM placement: $166	"In both ASC ($17 613 vs $18 194) and OHD ($19 832 vs $21 181) settings, single-stage SNM placement was less costly than 2-stage placement. The minimum SNM	Sensitivity analysis: single-stage SNM removal rates: "[…] even if 100% of devices were assumed to be removed, a single-stage approach

				Single-stage SNM placement: $770 Fluoroscopy for lead placement: $9 Lead removal: $148 Lead and generator removal: $213 **Facility fee—ASC** Stage-1 SNM placement: $4,681 Stage-2 SNM placement: 16,004 Single-stage SNM placement: $16,004 Fluoroscopy for lead placement: $39 Lead removal: $1,455 Lead and generator removal: $1,455 **Facility fee—OHD** Stage-1 SNM placement: $5,745 Stage-2 SNM placement: 17,803 Single-stage SNM placement: $17,803 Fluoroscopy for lead placement: $226 Lead removal: $2,690 Lead and generator removal: $2,690	success rates to achieve savings with a single-stage approach occur at 65.4% and 61.3% for ASC and OHD, respectively.“	would still be less costly than a two-stage approach for our base cases in both the ASC and OHD settings. In an ASC setting, if a 0% removal rate is assumed, an SNM success rate of 64% or higher is needed to make a single-stage approach less costly. If a 100% removal rate is assumed, the threshold success rate increases to 68%. In an OHD setting, if a 0% removal rate is assumed, an SNM success rate of 58% or higher is needed to make a single-stage approach less costly, while if a 100% removal rate is assumed, the threshold success rate increases to 65%” Sensitivity analysis: increased reimbursement: ”If 50% reimbursement is

				Anaesthesia fee Stage-1 SNM placement: $287 Stage-2 SNM placement: 198 Single-stage SNM placement: $287 Lead removal: $176 Lead and generator removal: $176		assumed, SNM success rates of at least 79.5% (ASC) and 77.3% (OHD) are needed to make a single-stage approach less costly. If 100% reimbursement is assumed, SNM success rates must further increase to 93.5% (ASC) and 93.2% (OHD).“ ”Using Medicare reimbursement, single-stage SNM placement is likely to be less costly than 2-stage placement for most practitioners. The savings are tied to SNM success rates and reimbursement rates, with reduced costs up to $5014 per case in centers of excellence (≥ 90% success).“
Cost Analysis of Interventions for Antimuscarinic Refractory Patients with Overactive	Watanabe et al. 2010,	Antimuscarinic refractory OAB patients in the US (payer perspective)	Intervention: Sacral neuromodulation (SNM), Comparator:	Input Costs inexplicable – Only AE base case costs and following explanation taken	”Three years after initiating treatment, the cumulative cost was [for SNM, intra-detrusor injection of	“Sensitivity analyses revealed that SNM persisted as the most costly intervention in all

Bladder (Watanabe et al. 2010)			Intra-detrusor botulinum toxin A (BoNTA) and augmentation cystoplasty (AC)	from the abstract could be extracted: "Costs (2007 US dollars) were calculated using Current Procedural Terminology (CPT) codes, Ambulatory Payment Classification (APC) codes; Diagnosis Related Group (DRG) payments, and Healthcare Common Procedure Coding System (HCPCS) Level II Codes extracted from the literature and from the SNM device manufacturer. CPT codes were converted to costs using the Center for Medicare and Medicaid Services (CMS) Relative Value Unit (RVU) fee schedule."	BoNTA, and AC] $26,269, $7651, and $14,337 respectively."	scenarios. The 3-year cumulative cost range produced by the sensitivity analyses for SNM, BoNTA, and AC was $25,384-$27,357, $4586-$11,476, and $12,315- $16,830, respectively." "All estimates of cost endpoints for SNM were greater than those for BoNTA and AC. These cost estimates, when combined with data on outcomes and risks, are important components of a robust health care technology assessment of antimuscarinic treatment failure options."
Mirabegron for the treatment of overactive bladder: cost-effectiveness from US commercial	Wielage et al., 2016	Patients with overactive bladder syndrome (OAB). Commercial payer: only 2% of patients	Mirabegron was compared to six antimuscarinic treatments commonly used for	Mirabegron $276.18, Fesoterodine $232.94, Oxybutynin $53.13, Solifenacin $268.87, Tolterodine	Commercial payer Solifenacin: $6,502, 2.418 QALY, dom.	One-way sensitivity analyses demonstrated the model was most sensitive to the cost

health-plan and Medicare Advantage perspectives		older than 65 years. Medicare plan: 16.8% disabled less than 65 years of age, and 83.2% aged 65 and older.	OAB in the US: fesoterodine, oxybutynin, solifenacin, tolterodine extended release (ER), tolterodine immediate release (IR), and trospium.	ER $195.79, Tolterodine IR $97.57, Trospium $164.13. Comorbidity (per episode): Depression $314.13 + $112.38, Skin rash $37.26 + $112.38 Urinary tract infection $92.69 + $112.38. Tibial nerve stimulation: Initial $1,999.00, Remaining 1st year $3,815.00, Additional year $2,358.00. Sacral neuromodulation: Initial testing $2,094.00, Remaining 1st year $26,586.00, Additional year $616.00. OnabotulinumtoxinA 6-week treatment $579.00 + $582.00. $0.23 Visits: Primary care $112.38, Outpatient $214.83,	Mirabegron: $6,494 2.429 QALY, $59,690 ICER Tolterodine ER: $5,255, 2.397 QALY, dom. Fesoterodine: $5,010, 2.384 QALY, dom. Trospium: $4,801, 2.399 QALY, dom. Tolterodine IR: $4,169, 2.390 QALY,$36,871 ICER Oxybutynin: $3,808 2.380 QALY, BASE <u>Medicare</u> Mirabegron: $ 6,516 2.343 QALY, $66,347 ICER Solifenacin: $6,420, 2.334 QALY, dom. Tolterodine ER: $5,224, 2.314 QALY, dom. Fesoterodine: $5,017, 2.303 QALY, dom. Trospium: $4,789, 2.317 QALY, dom. Tolterodine IR: $4,117, 2.308 QALY,$38,068 ICER Oxybutynin: $3,831 2.299 QALY, BASE	of mirabegron and the choice of network meta-analysis used to develop the transition probabilities. PSA estimated a 100% probability that mirabegron met a $100,000 WTP threshold from the commercial health plan perspective. The cost-effectiveness acceptability curve also illustrates a 27% probability of meeting a WTP of $50,000 per QALY, a 74% probability of meeting a $60,000 WTP per QALY, and a 95% probability of meeting a $70,000 WTP per QALY. Results from a Medicare perspective were similar. Mirabegron is a cost-effective alternative to antimuscarinics for OAB treatment.

				Emergency department $800.05, Miscellaneous: Incontinence pad $0.23		
Comparing Direct Medical Costs of OnabotulinumtoxinA With Other Common Overactive Bladder Interventions	Yehoshua, et al., 2018	Patients with overactive bladder syndrome (OAB), perspective of a commercial US payer	onabotulinumtoxinA 100 units injection vs. Enablex (darifenacin) 7.5 mg daily; Toviaz (fesoterodine fumarate) 4 mg or 8 mg once daily; Myrbetriq (mirabegron) 50 mg once daily; oxybutynin chloride IR (immediate release) 5 mg twice daily; Ditropan XL (oxybutynin chloride extended release) 10 mg once daily; Gelnique (oxybutynin chloride) 10% gel once daily; Vesicare (solifenacin) 5 mg or 10 mg daily; tolterodine IR (immediate release) 2 mg twice daily; tolterodine LA (long acting) 4 mg once daily; Detrol LA	Annual drug costs: MYRBETRIQ (mirabegron): $3076.28. DETROL LA (solifenacin): $3293.39. ENABLEX (darifenacin): $3018.21.VESIcare (solifenacin): $2746.57. TOVIAZ (fesoterodine fumarate): $2603.54. SANCTURA XR (trospium chloride): $2323.90. DITROPAN XL: $2156.40. OnabotulinumtoxinA: $956.32. Tolterodine LA: $1797.03. Tolterodine IR: $1534.05. Trospium chloride: $741.46. Oxybutynin chloride: IR: $321.42. Total annual costs of SNS: $19,443 for year 1, $468 for years 2–10 revisions / PTNS: $3395 for year 1,	Total cost of anticholinergics over 1 year ranged from $500 (oxybutynin chloride IR to $3472 (Detrol LA), and the cost of mirabegron was $3266. At years 5 and 10, the costs of anticholinergic treatment ranged from $2500 and $5000 (oxybutynin chloride IR), to $17,360 and $34,720 (Detrol LA), and the costs of mirabegron were $16,330 and $32,660. OnabotulinumtoxinA was associated with a total annual cost of $1892. Year 1 costs for device-treatments were, $3395 (PTNS), and $19,443 (SNS). At years 5 and 10, respectively, the costs were as follows: $9458 and $18,916 (onabotulinumtoxinA);	Sensitivity analysis exploring the impact of OnabotulinumtoxinA administration split between the physician office (60%), ASC (25%), and hospital outpatient (15%) settings, the total annual cost for onabotulinumtoxinA treatment was $2505, which was still less expensive than all branded medications except for Sanctura XR and Ditropan XL, and more costly than the 4 generic anticholinergics.

			(tolterodine long-acting) 4 mg once daily; trospium chloride IR 20 mg twice daily; and Sanctura XR (trospium chloride extended release) 60 mg once daily, SNS device implantation, and PTNS.	$2114 for years 2–10.	$11,849 and $21,316 (PTNS); and $21,316 and $33,801 (SNS).	

2 Details of relevant studies

Please give details of all relevant studies (all studies in table 1). Copy and paste a new table into the document for each study. Please use 1 table per study.

Cost-Effectiveness of Sacral Neuromodulation Compared to Botulinum Neurotoxin A or Continued Medical Management in Refractory Overactive Bladder (Arlandis et al. 2011)	
What are main differences in resource use and clinical outcomes between the technologies?	"[…] at 10 years, the cumulative costs of SNM, BoNT-A, and OMT were €29,166, €29,458, and €29,370, respectively, with cumulative QALYs of 6.89, 6.38, and 5.12." "Furthermore, ICERs for incontinence episode avoided at 10 years also demonstrate economic dominance for SNM compared to BoNT-A and OMT."
How are the findings relevant to the decision problem?	This study evaluated the incremental effects of sacral neuromodulation with an older device generation. While clinical effects will be comparable, costs might differ with the new technology in the following way: maintenance costs will be lower given that the new device does not need a new generator every four to five years.
Does this evidence support any of the claimed benefits for the technology? If so, which?	No, because study does not address the question studied in the current analysis. However, the evidence supports the general notion that SNM is a cost-effective intervention for treatment of OAB. It also reports non-rechargeable device lifetime in line with the current analysis' assumptions.
Will any information from this study be used in the economic model?	No.
What cost analysis was done in the study? Please explain the results.	Cost-effectiveness analysis results: "Results of the CEA […] indicate that, from a medium-term perspective, ICER estimates for SNM are €3775 compared to BoNT-A and €3412 compared to OMT at 5 years, whereas ICERs at 7 years (which accounts for an SNM generator replacement) are €9830 and €3433 compared to BoNT-A and OMT, respectively. These results suggest cost-effectiveness for SNM in the medium term given that the ICERs are well within the

Cost-Effectiveness of Sacral Neuromodulation Compared to Botulinum Neurotoxin A or Continued Medical Management in Refractory Overactive Bladder (Arlandis et al. 2011)	
	€30,000 cost-effectiveness threshold, which is deemed as efficient in Spain […]. Additionally, at 10 years, the cumulative costs of SNM, BoNT-A, and OMT are €29,166, €29,458, and €29,370, respectively, with cumulative QALYs of 6.89, 6.38, and 5.12. Thus, the relative cost savings for SNM, coupled with its enhanced outcomes compared to either treatment, demonstrate that SNM is the economically dominant treatment option in a 10-year time frame. Furthermore, ICERs for incontinence episode avoided at 10 years also demonstrate economic dominance for SNM compared to BoNT-A and OMT." Budget Impact Analysis results: The budget impact analysis showed an increment of 0.2% to 1.25% in total costs and is considered to be small in Spain in the evaluated 4 years.
What are the limitations of this evidence?	The limitations are that "treatment outcome assumptions are based on different sources and levels of evidence".
How was the study funded?	Funding by Medtronic International Sarl, Tolochenaz, Switzerland.

Sacral neuromodulation and Botulinum toxin A for refractory idiopathic overactive bladder: a cost-utility analysis in the perspective of Italian Healthcare System (Bertapelle et al. 2015)	
What are main differences in resource use and clinical outcomes between the technologies?	„[…] at year ten: cumulative costs were €32,975 for early SNM and €33,309 for early BTXA, while cumulative QALYs were 7.52 and 6.93, respectively.“ Subsequently, the ICUR showed dominance of the SNM strategy. Additionally, “ […] SNM appears to be cost effective (i.e. under €40,000/QALY) from year three (€21,259/QALY) onwards onwards […]”
How are the findings relevant to the decision problem?	This study evaluated the incremental effects of sacral neuromodulation with an older device generation. While clinical effects will be comparable, costs might differ with the new technology in the following way: maintenance costs will be lower given that the new device does not need a new generator every four to five years.
Does this evidence support any of the claimed benefits for the technology? If so, which?	No, because study does not address the question studied in the current analysis. However, the evidence supports the general notion that SNM is a cost-effective, and possibly dominant intervention for treatment of OAB.
Will any information from this study be used in the economic model?	No.
What cost analysis was done in the study? Please explain the results.	Cost-utility analysis results: “[…] with respect to the BoNT/A strategy, early SNM generates a per-patient QALY gain of 0.30 at year five and of 0.42 at year seven; additional costs are €1,804.48 and €2,874.76 at year five and seven (accounting for battery replacement), respectively. The corresponding ICURs are equal to €6,032.02 at year five and to €6,822.63 at year seven, well below the cost-effectiveness threshold considered. At year ten, a 0.59 QALY gain corresponds to a total saving of €333.22, making the “SNM strategy” economically dominant.”
What are the limitations of this evidence?	Given limitations encompass that only a binary semi-Markov model was used, “the analysis has been undertaken from the perspective of the third-party payer and not from the societal point of view, as recommended by the Italian guidelines for economic evaluations” and “data were retrieved

Sacral neuromodulation and Botulinum toxin A for refractory idiopathic overactive bladder: a cost-utility analysis in the perspective of Italian Healthcare System (Bertapelle et al. 2015)	
	from multiple sources with different levels of evidence."
How was the study funded?	"The economic evaluation was conducted by a Private Company, MSc, Creativ-Ceutical, Milan, Italy, supported by a grant by Medtronic, which never interfered with the evaluation of data and the results of the study."

Real world performance of SNM and onabotulinumtoxinA for OAB: Focus on safety and cost (Chughtai et al. unpublished)	
What are main differences in resource use and clinical outcomes between the technologies?	"After propensity score matching, onabotulinumtoxinA patients had a higher risk of 30-day complications including urinary tract infection (RR: 3.60 [1.34-9.70], p<0.01), hematuria (RR: 5.00 [1.71-14.63], P<0.01), urinary retention (RR: 3.25 [1.06-9.97], P=0.03) and had a higher risk of ER visit (RR: 1.67 [1.22-2.30], P<0.01) during 30 days when compared to SNM use." "SNM implantation led to frequent re-interventions at one and three years and was more expensive compared to OnabotulinumtoxinA injection. However, OnabotulinumtoxinA had higher rate of complications when compared to SNM."
How are the findings relevant to the decision problem?	Not directly, as the current analysis focuses on the cost implications of rechargeable vs. non-rechargeable SNM.
Does this evidence support any of the claimed benefits for the technology? If so, which?	No, because study does not address the question studied in the current analysis.
Will any information from this study be used in the economic model?	No.
What cost analysis was done in the study? Please explain the results.	Cost-cost analysis – The results indicate that SNM therapy is less cost effective in the short term, however a long-term analysis was not performed. On the other hand, onabotulinumtoxinA had a higher complication rate, which can lead to additional costs not considered in this study.
What are the limitations of this evidence?	Injection rates in the onabotulinumtoxinA group may vary depending on the setting in the hospital or ambulatory care and office settings. "There were some limitations in using claims-based data, including the fact that the severity of OAB cannot be captured." "Potential unmeasured confounding, such as physicians' and patients' preferences, may have created limitations to the observational study design. In addition, miscoding and under-coding may have occurred and the follow-up of patients

Real world performance of SNM and onabotulinumtoxinA for OAB: Focus on safety and cost (Chughtai et al. unpublished)	
	may also be incomplete because of the use of a state database." Long-term outcomes were not available.
How was the study funded?	Bilal Chughtai is an instructor/ consultant for Allergan

OnabotulinumtoxinA in the treatment of overactive bladder: a cost-effectiveness analysis versus best supportive care in England and Wales (Freemantle et al. 2016)	
What are main differences in resource use and clinical outcomes between the technologies?	”The total discounted cost per patient over the 10-year period was £10,160 with onabotulinumtoxinA and £11,572 with BSC. Total QALYs were 6.908 with onabotulinumtoxinA and 6.695 with BSC.“ The ICER showed dominance in all but two scenarios. However, in both cases OnabotulinumtoxinA was cost-effective.
How are the findings relevant to the decision problem?	This study has demonstrated the cost-effectiveness of onabotulinumtoxinA compared with best supportive care in the NHS setting of England and Wales. The results are expected to be generalisable to other healthcare systems.
Does this evidence support any of the claimed benefits for the technology? If so, which?	No, because study does not address the question studied in the current analysis.
Will any information from this study be used in the economic model?	The resource utilization assumption of SNM as the second-line therapy in the Freemantle analysis were used to compare and confirm the assumptions of the current analysis.
What cost analysis was done in the study? Please explain the results.	Cost-effectiveness study: “In the base-case analysis, onabotulinumtoxinA was associated with greater benefit and lower cost than BSC and was therefore the economically dominant treatment option.” The results were robust throughout the probabilistic sensitivity analysis,”
What are the limitations of this evidence?	Given limitations encompass “the lack of long-term consequences of poorly managed OAB and UI”, abandonment of results from some studies with follow-up of up to 8-years, not included new treatment options like mirabegron and due to utilization of RCTs as sources the external validity might haven not been demonstrated.
How was the study funded?	This project was funded by Allergan Inc.

Economic evaluation of sacral neuromodulation in overactive bladder: A Canadian perspective (Hassouna and Sadri, 2015)	
What are main differences in resource use and clinical outcomes between the technologies?	"Efficacy declined at a moderate rate (0-15% range) from 90% at year 1 to 75% at year 10. BonT-A treatment success rate declined more rapidly (range: 0–30%) from 80% at year 1 to 50% at year 10. OMT treatment rate remained the lowest and static at 4% throughout the treatment period (Table 1). The annual dropout rate, which may be attributed to adverse events or lack of efficacy, is defined as 7.5% for SNM and 2% for BonT-A. Probability values for urinary tract infection for BonT-A, OMT, and SNM were 23%, 12%, and 0% respectively" "The annual incremental cost of SNM vs. BonT-A was $7237 in year 1 and -$9402 in year 10 and was between $8878 and -$11 447 vs. OMT." "The annual (year 1–10) incremental quality-adjusted life years for SNM vs. BonT-A was 0.05 to 0.51 and SNM vs. OMT was 0.19 to 1.76."
How are the findings relevant to the decision problem?	This study evaluated the incremental effects of sacral neuromodulation with an older device generation. While clinical effects will be comparable, costs might differ with the new technology in the following way: maintenance costs will be lower given that the new device does not need a new generator every four to five years.
Does this evidence support any of the claimed benefits for the technology? If so, which?	No, because study does not address the question studied in the current analysis. However, the authors of this earlier study allude to the fact that maintenance costs will be lower with future generations of devices that have a longer lifetime.
Will any information from this study be used in the economic model?	No.
What cost analysis was done in the study? Please explain the results.	Cost-Utility-Analysis: "[…] SNM initially gains an advantage during the 4-year period and dominates at the 5-year mark. Analysis of SNM in comparison with OMT after 10 years reveals that SNM is definitively cost-effective

Economic evaluation of sacral neuromodulation in overactive bladder: A Canadian perspective (Hassouna and Sadri, 2015)	
	at the 2-year period and dominant at 5 and 10 years."
What are the limitations of this evidence?	Given limitations encompass missing inclusion of long-term side effects, "efficacy, utility scores and annual drop-out rates were constant, which may not represent real practice", "use of generic quality of life questionnaires", the choice of a third-party payer perspective instead of a societal perspective and the generalisability of the study.
How was the study funded?	Medtronic of Canada

Cost-Effectiveness of Test Phase Implantation Strategies for InterStim® Sacral Neuromodulation (Kantartzis and Shepherd, 2013)	
What are main differences in resource use and clinical outcomes between the technologies?	Reported total cost and total QALYs over the 54-month modelling cycle were: No InterStim® treatment: $24,409 and 3.420 QALYs Unilateral placement using PNE: $26,948 and 4.036 QALYs Unilateral stage I placement of permanent electrode leads: $27,169 and 4.201 QALYs Bilateral stage I placement of permanent electrode leads: $28,081 and 4.321 QALYs Bilateral placement using PNE: $28,136 and 4.104 QALYs Combined stage I and II placement with no testing phase: $31,824 and 4.113 QALYs "Bilateral PNE and combined stage I/II were excluded from cost-effectiveness calculations by simple dominance as there were options which were more effective and less expensive than both of these. Unilateral PNE was excluded by extended dominance. Both unilateral stage I and bilateral stage I were cost-effective options with ICERs of $3533 and $7600, respectively."
How are the findings relevant to the decision problem?	No, as the current analysis focuses on the cost implications of rechargeable vs. non-rechargeable SNM, and is not concerned with different testing strategies.
Does this evidence support any of the claimed benefits for the technology? If so, which?	No, because study does not address the question studied in the current analysis.
Will any information from this study be used in the economic model?	No.
What cost analysis was done in the study? Please explain the results.	Cost-effectiveness analysis: "Unilateral and bilateral stage I were the only cost-effective options with incremental cost-effectiveness ratios of $3533 and $7600, respectively. Because bilateral stage I was more effective, it is preferred."
What are the limitations of this evidence?	Given limitations encompass that the societal perspective used in the model "may not reflect the costs by an individual patient who may wish to avoid 2 insurance copays from 2 operative procedures"

Cost-Effectiveness of Test Phase Implantation Strategies for InterStim® Sacral Neuromodulation (Kantartzis and Shepherd, 2013)	
	and only “costs of chronic urinary incontinence and implantation, revision, and removal of the IPG and leads were considered.”
How was the study funded?	Funding by Medtronic

Cost-effectiveness analysis of sacral neuromodulation and botulinum toxin A treatment for patients with idiopathic overactive bladder (Leong et al. 2010)	
What are main differences in resource use and clinical outcomes between the technologies?	At year ten the cumulative costs were €36.878 for SNM therapy and €31.485 for BTX therapy, while cumulative QALYs were 8.69 and 8.32, respectively. This results in an ICER of €14.493 per QALY.
How are the findings relevant to the decision problem?	This study evaluated the incremental effects of sacral neuromodulation with an older device generation. While clinical effects will be comparable, costs might differ with the new technology in the following way: maintenance costs will be lower given that the new device does not need a new generator every four to five years.
Does this evidence support any of the claimed benefits for the technology? If so, which?	No, because study does not address the question studied in the current analysis. However, these findings suggest that SNM therapy is a cost-effective intervention when compared to BTX therapy, when considering analysis horizons longer than 5 years.
Will any information from this study be used in the economic model?	No.
What cost analysis was done in the study? Please explain the results.	Cost-effectiveness analysis: “Starting with SNM, treatment is cost-effective after 5 years compared to BTX. However, in some scenarios, such as the use of local anaesthesia for BTX treatment and SNM peripheral nerve evaluation or bilateral test, SNM was not cost-effective.”
What are the limitations of this evidence?	Given limitations encompass that “keeping the effect rate, the utility values and the yearly drop-out rate constant between 1 and 10 years may not be an accurate representation of the real treatment benefit” and the utility values assigned in this study are based on one study which used the Health Utility Index 3 questionnaire which might not be a true representation for OAB patients, however to the authors knowledge “no other relevant utility values are published”.
How was the study funded?	Financial support was provided by WAMU foundation (partners: Novartis, Medtronic, GlaxoSmithKline, Coloplast, AstraZeneca, Astellas, Abbot)

Outcome and Cost Analysis of Sacral Nerve Modulation for Treating Urinary and/or Fecal Incontinence (Leroi et al. 2011)	
What are main differences in resource use and clinical outcomes between the technologies?	"The median overall cost per patient in the first 2 years after the SNM treatment was € 16,403 [n=78] for patients implanted for urge urinary incontinence […]" "The adjusted cost analysis revealed that treating urge urinary incontinence with SNM costed an average of € 8525 more per participant the first 2 years (95% CI, € 6686–€ 10,364) than alternative treatments (P = 0.001)." Urge UI patients – SF-36 scores at 24 months (Implanted vs nonimplanted): Physical component summary: 44 vs 39 Mental component summary: 44 vs 39
How are the findings relevant to the decision problem?	This study evaluated the incremental effects of sacral neuromodulation with an older device generation. While clinical effects will be comparable, costs might differ with the new technology in the following way: maintenance costs will be lower given that the new device does not need a new generator every four to five years.
Does this evidence support any of the claimed benefits for the technology? If so, which?	No, because study does not address the question studied in the current analysis.
Will any information from this study be used in the economic model?	No.
What cost analysis was done in the study? Please explain the results.	Cost-effectiveness analysis: "Our prospective multicenter cohort study confirmed that, compared to alternative treatments, SNM improves urinary […] incontinence and QOL. The median cost of SNM for urge urinary incontinence was €16,403 per patient for the first 2 years. Using a more than 50% improvement in urge urinary continence as the effectiveness unit, ICER was estimated at €94,204 per patient at the 24-month follow-up. In addition, SNM had an ICER of €110,741 per QALY gained [at 12 months]. However, despite its costs, SNM was not dominated because it was significantly more effective than alternative treatments." "The average cost of SNM for urge urinary incontinence was € 8525 (95% confidence interval,

Outcome and Cost Analysis of Sacral Nerve Modulation for Treating Urinary and/or Fecal Incontinence (Leroi et al. 2011)	
	€ 6686–€ 10,364; P = 0.001) more for the first 2 years compared to alternative treatments."
What are the limitations of this evidence?	Limitations of the study are "associated with the design of this clinical study (i.e. lack of control group and not all costs being taken into account)" – no RCT, significant attrition rate of 47.1%, "the SNM cost-effectiveness values for implanted patients might not be completely accurate", use of a generic SF-36 QoL questionnaire instead of a urinary specific questionnaire, "Inaccuracies may also have occurred in the measurement of symptom improvement" and lastly the short time period of two years. Limitation pertaining to faecal incontinence: *"[…] an underestimation of the cost of SNM and an overestimation of its efficacy cannot be excluded. The data in this study were not collected prospectively for an economic evaluation. Costs were based on assumptions that could have biased the calculations. Also, the costs of conservative treatments were based on baseline prestimulation data that were considered to be equivalent to the continued use of conservative treatments. Preimplantation costs may have been higher because of more medical examinations and visits for the implantation.")*
How was the study funded?	Funding by the French National Ministry of Health

Cost of Neuromodulation Therapies for Overactive Bladder: Percutaneous Tibial Nerve Stimulation Versus Sacral Nerve Stimulation (Martinson, MacDiarmid and Black, 2013)	
What are main differences in resource use and clinical outcomes between the technologies?	”Costs differed markedly after SNS implantation with costs per patient […] more than 3 times higher at 2 years ($14,160 for SNS vs $3,850 for PTNS). “Effectiveness was measured as the percent of patients still on therapy at a given time.” “At 2 years 48% of patients continued on PTNS compared to 49% on SNS.” ICER: “In the base case the cost per additional patient treated with SNS was approximately $537,000 during 2 years.”
How are the findings relevant to the decision problem?	They are not relevant, as the current analysis focuses on the cost implications of rechargeable vs. non-rechargeable SNM, and is not concerned with comparison to TNS.
Does this evidence support any of the claimed benefits for the technology? If so, which?	No.
Will any information from this study be used in the economic model?	No.
What cost analysis was done in the study? Please explain the results.	Cost-effectiveness model: “To choose SNS over PTNS payers must find the ICER ($573,000 during 2 years per additional patient on therapy) to be a good price for the benefit.” “This study demonstrates that PTNS is a cost-effective way to deliver neuromodulation treatment for patients with OAB refractory to conservative and drug therapy.”
What are the limitations of this evidence?	“[…] the model did not include costs for minor complications or persistent incontinence […]” This CEA considered only short-term Costs and Outcomes.
How was the study funded?	Existing financial interest and/or other relationship with: Uroplasty (by Martinson and Black), Astellas, Pfizer, Watson and Allergan by MacDiarmid

Cost–effectiveness of overactive bladder treatments: from the US payer perspective (Murray et al. 2019)	
What are main differences in resource use and clinical outcomes between the technologies?	"Based on a 10-year time horizon, the estimated number of UIEs per patient per year for the evaluated treatments ranged from 1076 for onabotA 100U to 1480 for BSC (Table 2). The costliest therapy was SNS at $27,823 per patient over 10 years and the least expensive was BSC at $11,460 per patient. Total number of QALYs gained was greatest for patients receiving onabotA 100U (7.179) compared with BSC (7.069)." "Treatment with onabotA 100U was most cost-effective relative to BSC, with an estimated ICER of $32,680/QALY gained. The next lowest ICER/QALY gained was observed for PTNS ($71,126). Compared with BSC, all other assessed treatments yielded an ICER above the $100,000 threshold."
How are the findings relevant to the decision problem?	Not relevant, as the current analysis focuses on the cost implications of rechargeable vs. non-rechargeable SNM.
Does this evidence support any of the claimed benefits for the technology? If so, which?	No, because study does not address the question studied in the current analysis.
Will any information from this study be used in the economic model?	No.
What cost analysis was done in the study? Please explain the results.	"The results of this study show that when compared with BSC, onabotA is the most cost-effective therapy for refractory OAB from the US payer perspective relative to other available treatments, including SNS, PTNS, anticholinergic medications and mirabegron."
What are the limitations of this evidence?	"The model did not permit for the comparison of all six treatments simultaneously; […]" Given limitations of this study are: "The sensitivity analyses did not account for alternate patient pathways and disease progression through model health states by exploring scenarios with varying transition probabilities." "[…] potential heterogeneity within the examined patient population was not considered […]"

Cost–effectiveness of overactive bladder treatments: from the US payer perspective (Murray et al. 2019)	
How was the study funded?	Funding by Allergan plc.

Comparison of patients undergoing a two-stage sacral nerve stimulation procedure: is there a cost benefit for a single-stage procedure? (Nikolavsky et al. 2011)	
What are main differences in resource use and clinical outcomes between the technologies?	"Total Medicare and Blue Cross/Blue Shield (BCBS) reimbursement for a two-stage procedure was calculated at $21,428/case and $26,968. Implanting the lead and generator as a single-stage would cost Medicare and BCBS $20,696 and $21,602, respectively."
How are the findings relevant to the decision problem?	They are not relevant.
Does this evidence support any of the claimed benefits for the technology? If so, which?	No, because study does not address the question studied in the current analysis.
Will any information from this study be used in the economic model?	No.
What cost analysis was done in the study? Please explain the results.	Cost-cost analysis: Results of this study suggest that "[…] a single-stage approach would yield savings of $3,655/case (BC/BS) over a two-stage approach (after the cost of explantation is factored in)." "Due to differences in reimbursement, the cost savings are not seen in the Medicare population. Assuming a conversion rate of Stage 1 to Stage 2 of 90.3%, there is a net loss of $806 in Medicare patients."
What are the limitations of this evidence?	"[…] the analysis did not factor in other economic benefits of a single-stage procedure such as reducing time taken off work, minimizing infection rate by not having an external lead, cost of travel, cost of additional antibiotics, and pain control medications required for a two-stage procedure." Another limitation is that the results are not generalizable, since the rate of implantation and costs/ reimbursements for health care systems, therefore break-even points vary significantly.
How was the study funded?	Funding unclear

Cost Profiles and Budget Impact of Rechargeable Versus Non-Rechargeable Sacral Neuromodulation Devices in the Treatment of Overactive Bladder Syndrome (Noblett et al. 2017)	
What are main differences in resource use and clinical outcomes between the technologies?	"At base-case assumptions, discounted 15-year costs for the non-rechargeable and rechargeable strategies were $64,111 and $36,990, respectively, resulting in total cost savings for the rechargeable strategy of $27,121 […]." Budget-Impact-Analysis: "Over the 15-year horizon, the gradual adoption scenario yielded potential discounted savings of $7.989 billion."
How are the findings relevant to the decision problem?	The findings are directly relevant to the decision problem, as they address a similar question in the context of the U.S. healthcare system.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes, this evidence supports the claimed benefit of a longer device lifetime, which is relevant to patients (reduced adverse events on basis of less replacement procedures) and importantly to healthcare payers (substantive cost reductions on basis of reduced need for device replacements).
Will any information from this study be used in the economic model?	Yes, the economic model used for the UK analysis is an adaptation of the publication model to the UK healthcare system context.
What cost analysis was done in the study? Please explain the results.	Cost-consequence study / Budget Impact Analysis: "Our findings suggest that, at current reimbursement rates, rechargeable neurostimulator device technology for sacral neuromodulation may deliver significant cost savings to payers over the course of treatment."
What are the limitations of this evidence?	The limitations of this analysis encompass, that rechargeable SNM devices are not commercially available, therefore information about long-term performance is lacking. The assumption of similar reimbursement payments for non-rechargeable and rechargeable systems, which is realistic but not definite. "Assumptions about the payer mix and site of care are based on expert opinion and data from one recent study". "Finally, the selection of a 15-year time horizon as the base case for this analysis is likely conservative […]"

Cost Profiles and Budget Impact of Rechargeable Versus Non-Rechargeable Sacral Neuromodulation Devices in the Treatment of Overactive Bladder Syndrome (Noblett et al. 2017)	
How was the study funded?	Grant sponsor was Axonics Modulation Technologies, Inc.

Sacral Nerve Stimulation For Urinary Urge Incontinence, Urgency-Frequency, Urinary Retention, and Fecal Incontinence (Medical Advisory Secretariat Ontario, 2005)	
What are main differences in resource use and clinical outcomes between the technologies?	There was no comparison between technologies, rather an estimation of costs for the management of urinary urge incontinence was performed.
How are the findings relevant to the decision problem?	The findings are not relevant, as they do not address the decision problem, and cost data come from a different country.
Does this evidence support any of the claimed benefits for the technology? If so, which?	No, because study does not address the question studied in the current analysis.
Will any information from this study be used in the economic model?	No.
What cost analysis was done in the study? Please explain the results.	Cost-Analysis: “Total costs in the Ontario-Based Economic Analysis determined that total costs were approximately $2,823 for Hospitalization Costs + $10,000 to $14,000 for Device Costs + $1,439 for OHIP physician costs.”
What are the limitations of this evidence?	The analysis is not generalizable. Limitations are not explicitly named.
How was the study funded?	HTA-report by Medical Advisory Secretariat, Ontario

Comparative effectiveness of one versus two-stage sacral neurostimulation device placement (Patel et al. 2019)	
What are main differences in resource use and clinical outcomes between the technologies?	A two-stage placement results in total initial procedure costs of $6,170. Patients having a successful conversion the reimbursement total was $18,474, if the conversion was unsuccessful reimbursement total was $2,879. A one-stage placement results in total initial procedure costs of $18,483. Patients having a successful conversion, no additional costs were assumed, if the conversion was unsuccessful reimbursement total was $5,758.
How are the findings relevant to the decision problem?	The findings are not directly relevant, as they concern different SNM testing strategies only.
Does this evidence support any of the claimed benefits for the technology? If so, which?	No, because study does not address the question studied in the current analysis.
Will any information from this study be used in the economic model?	No.
What cost analysis was done in the study? Please explain the results.	Cost-cost-Analysis: “Cost difference between one versus two-stage placement varied directly based on the rate of successful conversion. If the overall rate of successful conversion was low, a two-stage approach appeared to be the least expensive option. If the overall rate of successful conversion was high, a one-stage approach appeared to be the most cost-effective option. Specifically, if the conversion rate from testing phase to permanent placement is greater than 71%, utilization of a one-stage approach proved to be cost effective compared to a two-stage approach […].”
What are the limitations of this evidence?	The limitations of this analysis encompass using “reimbursement rates for outpatient procedures […] they may not accurately reflect charges and do not include patient related expenses”, “several benefits of a one-stage procedure” were not considered, “Medicare hospital outpatient reimbursements were assumed for our study”, percutaneous procedure were not included and lastly complication rates were assumed to be similar, which may vary between patient groups.

Comparative effectiveness of one versus two-stage sacral neurostimulation device placement (Patel et al. 2019)	
How was the study funded?	Funding unclear

Cost-Effectiveness of Sacral Neuromodulation Versus Intravesical Botulinum A Toxin for Treatment of Refractory Urge Incontinence (Siddiqui et al. 2009)	
What are main differences in resource use and clinical outcomes between the technologies?	”In the base case scenario sacral nerve stimulation was more expensive ($15,743 vs $4,392) and more effective (1.73 vs 1.63 quality adjusted life-years) than botulinum toxin A during a 2-year period. The incremental cost-effectiveness ratio was $116,427 per quality adjusted life-year.“
How are the findings relevant to the decision problem?	They are not relevant, as they concern only the comparison of SNM to Botox.
Does this evidence support any of the claimed benefits for the technology? If so, which?	No, because study does not address the question studied in the current analysis.
Will any information from this study be used in the economic model?	No.
What cost analysis was done in the study? Please explain the results.	Cost-Effectiveness Analysis: “Our analysis suggests that BoNT-A would be a cost-effective therapeutic option for refractory urge incontinence in the first 2 years of therapy.”
What are the limitations of this evidence?	The limitations of this study encompass a relatively short time period, due to lack of data indirect costs were not included and as in other decision analyses the model is depending on the quality of evidence.
How was the study funded?	Funding unclear

To stage or not to stage? — A cost minimization analysis of sacral neuromodulation placement strategies (Sun et al. 2019)	
What are main differences in resource use and clinical outcomes between the technologies?	”In both ASC ($17 613 vs $18 194) and OHD ($19 832 vs $21 181) settings, single-stage SNM placement was less costly than 2-stage placement. The minimum SNM success rates to achieve savings with a single-stage approach occur at 65.4% and 61.3% for ASC and OHD, respectively.“
How are the findings relevant to the decision problem?	They are not relevant, as they concern only the question whether single-stage or 2-stage placement is preferable.
Does this evidence support any of the claimed benefits for the technology? If so, which?	No, because study does not address the question studied in the current analysis.
Will any information from this study be used in the economic model?	No.
What cost analysis was done in the study? Please explain the results.	Cost-minimization Analysis: “Using Medicare reimbursement cost data, single-stage SNM placement is less costly than two-stage placement for most practitioners and should be considered as a standard approach. The savings are tied to SNM success rates and reimbursement rates, with the success in centers of excellence (~90%) saving up to $5014 per case. Further, a single-stage procedure optimizes utilization of healthcare and patient resources.”
What are the limitations of this evidence?	The limitations of this study encompass using a Medicare payment model, which might not be transferable to other insurers, using estimates of infection rates for single-stage placements and using the base-case single-stage infection rate for the second implantation again. Finally, a limitation of this study was “the practice of explanting all infected devices” instead of involving treatment with antibiotics.
How was the study funded?	No conflicts of interests declared.

Cost Analysis of Interventions for Antimuscarinic Refractory Patients With Overactive Bladder (Watanabe et al. 2010)	
What are main differences in resource use and clinical outcomes between the technologies?	”Three years after initiating treatment, the cumulative cost was [for SNM, intra-detrusor injection of BoNTA, and AC] $26,269, $7,651, and $14,337 respectively.“
How are the findings relevant to the decision problem?	They are not relevant, as they address a different decision problem in a different country context.
Does this evidence support any of the claimed benefits for the technology? If so, which?	No, because study does not address the question studied in the current analysis.
Will any information from this study be used in the economic model?	No.
What cost analysis was done in the study? Please explain the results.	Cost-analysis: “SNM cost exceeded intra-detrusor injection of BoNTA and AC for treatment of OAB. These cost disparities continue beyond year 1 from inception of treatment and persist at the end of year 3.”
What are the limitations of this evidence?	The limitations of this study encompass the short time period of 3 years analysed, cost estimations were based on literature sources and recent studies, costs might vary between insurers and if alternative Medicare reimbursement coding was used. Finally, this analysis does not include outpatient drugs.
How was the study funded?	Authors were sponsored in part by Allergan Inc.

Mirabegron for the treatment of overactive bladder: cost-effectiveness from US commercial health-plan and Medicare Advantage perspectives (Wielage et al. 2016)	
What are main differences in resource use and clinical outcomes between the technologies?	Mirabegron does not share the frequency of AEs or the ACB associated with antimuscarinic pharmacological OAB treatments. Persistence has been poor with all OAB antimuscarinics, while initial evidence suggests mirabegron may have a better persistence profile.
How are the findings relevant to the decision problem?	The findings are not relevant to the decision problem.
Does this evidence support any of the claimed benefits for the technology? If so, which?	No, because study does not address the question studied in the current analysis.
Will any information from this study be used in the economic model?	No.
What cost analysis was done in the study? Please explain the results.	Costs relied heavily on the prior work performed by Ko et al., Martinson et al., and Carlson et al. Medical costs calculated in these studies for previous years were inflated to November 2015 equivalents using the medical care component of the US Consumer Price Index.
What are the limitations of this evidence?	A simplifying assumption of the analysis concerned patients that discontinued in first line rather than switching to second-line oral treatment. Upon re-entry to treatment in our model these patients did not retry an oral treatment but proceeded directly to third line. This simplified the model but was contrary to patient baseline characteristics from trials of these third-line treatments, which report patients try multiple oral treatments before third-line. Because third-line therapies were modelled as having greater efficacy, this simplification rewarded initial oral treatments that had poor persistence. Thus, this simplification was also conservative.
How was the study funded?	Funded by Medical Affairs, Americas, Astellas Pharma Global Development, Northbrook, IL

Comparing Direct Medical Costs of OnabotulinumtoxinA With Other Common Overactive Bladder Interventions (Yehoshua et al. 2018)	
What are main differences in resource use and clinical outcomes between the technologies?	For the base case, only AE costs attributable to onabotulinumtoxinA were included. The total cost of using pharmaceutical medications included drug costs and 2 annual physician visits for follow-up. Additionally, for mirabegron, it was assumed that 13% of patients would be prescribed metoprolol based on an analysis of MarketScan claims data, and these patients would require 1 additional physician visit. The cost of SNS included cost of the device, device eligibility testing by peripheral nerve evaluation (PNE) and/or staged implantation, cost of permanent implantation, device maintenance (assuming patients receive 2 reprogramming visits per year), and cost of battery replacement at Year 7. Only a proportion of patients (51%) evaluated for SNS ultimately received a permanent implant.
How are the findings relevant to the decision problem?	The findings are not relevant to the decision problem.
Does this evidence support any of the claimed benefits for the technology? If so, which?	No, because study does not address the question studied in the current analysis.
Will any information from this study be used in the economic model?	No.
What cost analysis was done in the study? Please explain the results.	Comparison of annual costs of onabotulinumtoxinA 100 units (U) injection with 12 commonly used pharmaceutical treatments and 2 medical devices for OAB. Botox treatment with OnabotulinumtoxinA results in significantly lower total costs than PTNS and SNS at year 1 ($1892 vs. $3395 vs $19,443), year 5 ($9,458 vs. $11,849 vs $ 21,316) and year 10 ($18,916 vs. $22,417 vs. $33,801).
What are the limitations of this evidence?	The model did not include costs due to AEs for pharmaceutical treatments. The inclusion of AEs for onabotulinumtoxinA, but not for pharmaceutical comparators, resulted in an overestimate for cost of onabotulinumtoxinA in comparison with the costs of pharmaceutical treatments.

Comparing Direct Medical Costs of OnabotulinumtoxinA With Other Common Overactive Bladder Interventions (Yehoshua et al. 2018)	
	The assumption of battery replacement at 7 years for SNS may be conservative, as newer smaller batteries, based on usage, last 2.9 to 5.4 years. More frequent battery replacement of every 5 years for SNS yields an even less favourable long-term cost ($43,946 for SNS over 10 years).
How was the study funded?	This study was funded by Allergan, PLC.

3 Economic model

This section refers to the de novo economic model that you have submitted.

Description

Patients

Describe which patient groups are included in the model.

Patients with symptoms of overactive bladder, specifically people for whom conservative therapy and drug treatment have failed or are not suitable.

Technology and comparator(s)

State the technology and comparators used in the model. Provide a justification if the comparator used in the model is different to that in the scope.

Axonics sacral neuromodulation (SNM) system (Axonics Modulation Technologies, Inc. – rechargeable device) vs. other SNM system (InterStim, Medtronic, Inc. – a non-rechargeable device)

Model structure

Provide a diagram of the model structure you have chosen in Appendix B.

Justify the chosen structure of the model by referring to the clinical care pathway outlined in part 1, section 3 (Clinical context) of your submission.

Patients with overactive bladder syndrome who have not responded to conservative management or drug treatment, or who are unwilling to accept the possible risk of catheterisation with botulinum injection, are candidates for SNM. Our model compares the costs of the two SNM options (rechargeable vs. non-rechargeable), by following these patients over time, starting with the implantation of the device(s), and considering all relevant events and associated costs (adverse events, device replacement, cost for patients who have

discontinued therapy). In addition, a scenario analysis also explores the testing performed prior to implantation to evaluate whether patients respond to stimulation therapy.

As such, the model structure resembles the clinical pathway and events that may occur in the included patient group.

Table 2 Assumptions in the model

In this table, list the main assumptions in the model and justify why each has been used.

Assumption	Justification	Source
There are no differences in SNM therapy effectiveness and therapy discontinuation between Axonics rechargeable SNM and the other non-rechargeable SNM system (Interstim).	As has been demonstrated in the clinical submission, the fundamental SNM treatment mechanism is the same between the rechargeable and non-rechargeable system, and for the purpose of this cost comparison analysis, there is no reason to assume any differences in outcomes. Note: Differences in cumulative adverse events are considered separately, resulting from differences in the frequency of required stimulator replacement between the rechargeable and non-rechargeable technology (see below). The same holds for potential differences in required device explants, on the basis that the rechargeable device is compatible with full-body MRI, while the non-rechargeable device is not. This is explored in sensitivity analyses.	See clinical submission.
The device lifetime differs substantially between the rechargeable and non-rechargeable device, reducing substantially the need for device replacements with the	The Axonics device has a device lifetime of 15 years, while the non-rechargeable device has an average device lifetime of	Cameron et al, 2013 (stating InterStim lifetime of 4.4 yrs.)

rechargeable Axonics device. This not only leads to reduced costs for replacement procedures and devices, but also to a reduction in replacement procedure-related adverse events.	4.4 yrs, as evidenced by prior publications and device information shared by the manufacturer of InterStim. The open-ended 15 years life span of the Axonics Neurostimulator has been validated through extensive testing based on industry standards. Life span evaluation is performed by accelerated charge/discharge cycles and assessment of their impact on the Neurostimulator performance through time, in particular its charging time (duration of a charge) or charging interval (time need between 2 charges). The Axonics Neurostimulator battery has been tested through a total of 1,000 charge/discharge cycles with less than 20% loss in performance. For an average charging interval of 2 weeks (charging every 2 weeks), this corresponds to 40 years of life. For an average charging interval of 1 week (charging every week), this corresponds to almost 20 years of life (1,000 cycles / 52 weeks = 19.2 years). The Axonics Neurostimulator also contains smart software technology that limits charging intensity for protection against early degradation. On this basis, Axonics conservatively obtained CE mark approval for an open-ended duration of 15 years.	Noblett et al, 2017 (stating InterStim lifetime of 4.4 yrs., based on manufacturer information) For Axonics data, see explanation on left and in the clinical submission.

	The Axonics Tined Lead has also been validated for a 15 years life span based on the industry standard EN 45502-2-2:2008. Evaluation is performed through bending cycles simulating stress over time in an accelerated fashion. A 5 years conservative life span is anticipated for a lead resisting 47,000 bending cycles. The Axonics Tined Lead passed over 200,000 bending cycles, representing a life span of over 20 years. This data supported CE mark approval of the Axonics system for an open-ended life of 15 years.	
No differences are assumed between the rechargeable and the non-rechargeable system in the testing and test outcomes leading up to implantation of the full SNM system (i.e., whether or not a device is implanted and therapy initiated). As such, the base case calculations do not include testing leading up to implementation.	The work-up and testing approach is the same between both therapies. As such, there are no differences in costs or outcomes that would need to be considered. On this basis, the base case calculation/model only consider the actual implantation of the full systems. However, the model also facilitates a calculation that considers testing costs and outcomes. We explore these calculations in a scenario analysis, and the EAC has the ability to explore further calculations as needed using this analysis feature.	See clinical submission.

Table 3 Clinical parameters, patient and carer outcomes and system outcomes used in the model

In this table, describe the clinical parameters, patient and carer outcomes and system outcomes used in the model.

Parameter/outcomes	Source	Relevant results	Range or distribution	How are these values used in the model?
Patient age, yrs.	Noblett et al, 2016	57	43 to 71 (based on study-reported age of 57.0 ± 14.2 years)	Age at therapy initiation is used to calculate cohort survival over the analysis horizon, using latest lifetables for England. The percent of the cohort alive at any given time is important to facilitate proper cost accounting of replacement events and other management costs beyond the index procedure.
Therapy discontinuation, per 3-month cycle, first year	Noblett et al, 2016	1.22% (based on 4.7% (13/272 subjects) who discontinued therapy in the first year)	0.56–3.36%	This parameter, in conjunction with subsequent therapy discontinuation in following years, informs the calculation of the percent of patients on active therapy at any given time.
Therapy discontinuation, per 3-month cycle, second and following years	Chughtai et al, 2015	0.08% (based on information that 6.0% had discontinued therapy at 5 yrs., and 4.7% at one year, per above)	0.05–0.30%	See above
Implant site infection, index procedure	Brueseke et al, 2015	4.48%	2.20–19.10%	Informs the need for device removal and for i.v. antibiotic treatment, which are events associated with resource utilization.

Implant site infection, replacement procedure	Noblett et al, 2017	2.24% (50% of index procedure input, per clinical expert opinion)	1.10–9.55%	See above.
Surgical site pain requiring surgical intervention	Investigator-reported parameter, based on InSite study (Noblett et al, 2016)	4.04% (11 of 272 subjects in InSite)	2–10%	Informs the need for revision or explant, which are events associated with resource utilization.
Lead migration/dislodgment	Investigator-reported parameter, based on InSite study (Noblett et al, 2016)	1.10% (3 of 272 subjects in InSite)	0.55–2.20%	Informs the need to replace the lead, which is an event associated with resource utilization.
Lead fracture	Investigator-reported parameter, based on InSite study (Noblett et al, 2016)	1.47% (4 of 272 subjects in InSite)	0.5–5.0%	Informs the need to replace the lead, which is an event associated with resource utilization.

Required stimulator replacement, **non-rechargeable device**	Cameron et al., 2013	4.4 yrs.	2.0–7.0 yrs. (upper bound based on Freemantle et al, 2016 assumption)	Informs the frequency of required device replacements, a key input to the analysis (see also comments in “Main assumptions” above)

Required stimulator replacement, **rechargeable device (Axonics)**	Device lifetime for which therapy gained regulatory approval in the EU and in the U.S., based on comprehensive testing data.	15.0 yrs.	10.8* – 19.2 yrs. (upper bound is theoretical expected lifetime of the Axonics system, calculated on basis of an average charging interval of 1 week (charging every week, per instructions for use), which corresponds to 19.2 yrs. (1,000 cycles / 52 weeks)) ** the symmetric lower-bound value is a hypothetical assumption to test the effect of – fully hypothetical – lifetime shorter than approved minimum of 15 years. It was explored for analytical reasons, similar to the short 2-year survival assumption of InterStim in that device's respective analysis.*	Informs the frequency of required device replacements, a key input to the analysis (see also comments in "Main assumptions" above)

Programming visits, first year	Cameron et al, 2013	2.14	1.0-3.0	Informs resource utilization and related costs for patients on SNM. No difference between rechargeable and non-rechargeable assumed (in base case)
Programming visits, subsequent years	Cameron et al, 2013 (based on yr. 2 data)	0.74	1.0-3.0	Informs resource utilization and related costs for patients on SNM. No difference between rechargeable and non-rechargeable assumed (in base case)

If any outcomes listed in table 4 are extrapolated beyond the study follow-up periods, explain the assumptions that underpin this extrapolation.

Therapy discontinuation: The Chughtai et al. 2014 data, which form the basis for yrs. 2 and following based on 5-year reported data, are assumed to be maintained over the course of the patient's treatment. In the absence of more accurate data, this seems reasonable. Note also that using the current assumptions for yr. 1 and yrs. 2 and following leads to estimates of patients who have discontinued therapy in the long-run that is in line with the 7.0% assumed in Freemantle et al, 2016 for their UK analysis.

Programming visits in yrs. 2 and following: Model, conservatively, assumes the number of programming visits reported in yr. 2 of Cameron et al, 2013 is maintained in subsequent years. Note that the Cameron et al. data suggest a gradual decline in years 3 through 5, which was their maximum follow-up. However, as these visits apply equally to both strategies, different assumptions would not contribute to any meaningful cost difference.

Table 4 Other parameters in the model

Describe any other parameters in the model. Examples are provided in the table. You can adapt the parameters as needed.

Parameter	Description	Justification	Source
Time horizon	15 years	This time frame for the base case analysis was chosen as SNM therapy is intended as a long-term therapy, and as relevant costs to the healthcare system need to be appropriately captured. Any analysis horizon of less than 15 years would also omit the Axonics replacement costs, which occur after 15 years. This would introduce bias.	N/A
Discount rate	3.5% p.a.	NICE Guideline for CEA; Medical technologies guidance user guide	NHS MTG Methods Guide.
Perspective (NHS/PSS)	NHS, with PSS costs included for patients off-therapy	NHS is the decision maker and incurs essentially all costs for SNM therapy	Text
Cycle length	3 months	Provides sufficient granularity to appropriately consider costs incurred over the analysis time horizon.	Text
Transition probabilities: Mortality	Mortality is based on UK lifetables, with gender-specific mortality calculation. No mortality difference assumed to general population.	Mortality is an important parameter to reflect proper cost accounting in model. Clinical evidence does not suggest patients with OAB have higher mortality risk than general population.	Noblett et al, 2017

Transition probabilities: Therapy discontinuation	Two different therapy discontinuation probabilities were assumed. For the first year, 3-month probabilities were calculated from the one-year proportion of 4.7% reported in Noblett et al, 2016. For subsequent years, the difference between the Noblett one-year proportion and the Chughtai et al, 2014 proportion at 5 years (6%) was used to calculate a per-cycle discontinuation probability of 0.08% starting in year 2.	These data reflect best available evidence. The parameter was included as patients who discontinue therapy do no longer incur SNM cost, specifically replacement costs.	Noblett et al, 2016; Chughtai et al, 2015
Health states	The modelled Markov states are “on non-rechargeable SNM therapy,” “on rechargeable SNM therapy,” “off SNM therapy (discontinued),” and “death”	These health states were chosen as they provide the relevant inputs to conduct state-specific cost calculations by strategy. Note that adverse events, replacement events are calculated based on state-specific event rates.	Noblett et al, 2017
Sources of unit costs	NHS reference costs (for SNM implantation, replacement, explantation, programming, and other adverse events)	As SNM therapy for OAB is an established therapy in the NHS, with many years of history, all relevant procedural cost inputs are available as reference costs. As such, the unit costs are clearly defined. For device costs, which are added, the latest cost data from NHS Supply Chain are used (excl. VAT).	National Schedule of Reference Costs - Year 2017-18 - NHS trust and NHS foundation trusts
Proportion of device replacement needed in patients experiencing infection	37%	11 of 30 patients in the cited study required replacement.	Brueseke et al, 2015; Noblett et al, 2017

Proportion of i.v. antibiotic treatment needed in patients experiencing infection	30%	9 of 30 patients in the cited study required i.v. antibiotic treatment (which we assume will require an inpatient stay).	Brueseke et al, 2015; Noblett et al, 2017
Proportion of patients with surgical site pain who require revision	82%	9 of 11 patients in the cited study required revision.	Noblett et al, 2016; Noblett et al, 2017
Proportion of patients with surgical site pain who require explantation	18%	2 of 11 patients in the cited study required explantation.	Noblett et al, 2016; Noblett et al, 2017

Explain the transition matrix used in the model and the transformation of clinical outcomes, health states or other details.

As stated above, modelled Markov states are “on non-rechargeable SNM therapy,” “on rechargeable SNM therapy,” “off SNM therapy (discontinued),” and “death”.

The transition matrix is defined by the provided probabilities:

- Stage-specific mortality
- Per-cycle therapy discontinuation, stage-specific

Adverse events and resource utilization are calculated based on the following key input parameters:

- Therapy-specific device life
- Explantation rate(s)
- Stage-specific AE rates (tied to first cycle after index implant event and any subsequent replacement events)

Resource identification, measurement and valuation

Technology costs

Provide the list price for the technology (excluding VAT).

The list prices for both the rechargeable and non-rechargeable SNM therapies were obtained from NHS Supply Chain (Sept. 2019).

Below is the full price list of devices and accessories, excluding VAT.

	Axonics UK NHS SC	**Medtronic UK NHS SC**
Trial Stimulator Remote	£ 500.00	[redacted]
PNE kit	£ 300.00	[redacted]
Trial stimulator	£ 175.00	[redacted]
IPG	£ 7,000.00	[redacted]
TL	£ 1,600.00	[redacted]
TL extension	£ 300.00	£ -
TL Introducer kit	£ 500.00	[redacted]
Programmer	£ 500.00	[redacted]
Charger	£ 560.00	£ -

The combination of devices used for the various events and resulting costs used in the analysis are as follows:

Index implantation:

Non-rechargeable: IPG, TL, TL introducer kit: £7,474
Rechargeable: IPG, TL, TL introducer kit, charger: £9,660

Patient programmer (at index, and programmer replacement intervals):

Non-rechargeable: programmer: [redacted]
Rechargeable: programmer: £500

Device replacements:

Non-rechargeable: IPG: [redacted]
Rechargeable: IPG: £7,000

PNE (for testing calculations only):

Non-rechargeable: PNE kit, trial stimulator: £386
Rechargeable: PNE kit, trial stimulator: £475

Lead revision, OR Stage 2 tined lead (for testing calculations only):

Non-rechargeable: Trial stimulator, TL, TL Introducer kit: £1,778
Rechargeable: Trial stimulator, TL, TL extension, TL Introducer kit: £2,575

If the list price is not used in the model, provide the price used and a justification for the difference.

Only list prices excl. VAT are used.

NHS and unit costs

Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs, the national tariff and unit costs (from PSSRU and HSCIC). Please provide relevant codes and values (e.g. OPCS codes and ICD codes) for the operations, procedures and interventions included in the model.

As (non-rechargeable) SNM therapy is an established therapy in the NHS, all relevant codes and costs are established.

The same codes and costs also apply to rechargeable SNM therapy (Axonics).

ICD Code:

N328 Overactive bladder

OPCS Codes:

A70.1 Implantation of neurostimulator into peripheral nerve

A70.2 Maintenance of neurostimulator in peripheral nerve

A70.3 Removal of neurostimulator from peripheral nerve

A70.4 Insertion of neurostimulator electrodes into peripheral nerve

A70.7 Application of transcutaneous electrical nerve stimulator

Reference costs (all confirmed with current HRG4+ grouper):

Index implantation of stimulator (whole system):
HRG LB79Z 2017/18 Reference cost: £3,520 (inflated in model to 2019 using CPI Health)
Current NHS tariff: £2,490

Replacement of stimulator (at end of battery life):
HRG AA57A 2017/18 Reference cost: £670 (day case - inflated in model to 2019 using CPI Health)
Current NHS tariff: £590
Note: Cost, if inpatient (not day case): £3,077 (inflated in model to 2019)

SNM device removal:
HRG AA54C 2017/18 Reference cost: £2,372 (inflated in model to 2019 using CPI Health)
Current NHS tariff: £2,203

Outpatient programming:
HRG AA57A 2017/18 Reference cost (outpatient): £111 (inflated in model to 2019 using CPI Health)
Current NHS tariff: £94

PNE:
HRG LB80Z 2017/18 Reference cost (day case): £1,495 (inflated in model to 2019 using CPIHealth)
Current NHS tariff: £1,789

Stage 1 or Stage 2 tined lead implant:
HRG LB80Z 2017/18 Reference cost (day case): £1,495 (inflated in model to 2019 using CPIHealth)
Current NHS tariff: £1,789

i.v. antibiotic treatment (4 wks.) in case of sever device-related infection, assumed inpatient:
HRG WH07B 2017/18 Reference cost: £5,216 (inflated in model to 2019 using CPIHealth)
Current NHS tariff: £4,185

Lead revision:
HRG LB80Z 2017/18 Reference cost (day case): £1,495 (inflated in model to 2019 using CPIHealth)
Current NHS tariff: £1,789

Follow-up costs after index implant (in addition to any applicable adverse events mgmt.):
HRG WF01A 2017/18 Reference cost (day case): £105 (inflated in model to 2019 using CPIHealth)
Current NHS tariff: £1,789

Health care costs for patients who discontinued SNM therapy:

Cost of incontinence pads, per week: £8, per NICE CG 171 economic analysis, 2013
Cost of GP Surgery consultation: £37 (PSSRU 2018, assumption per NICE CG 171, 2013 – 6 times a year)

Resource use

Describe any relevant resource data for the NHS in England reported in published and unpublished studies. Provide sources and rationale if relevant. If a literature search was done to identify evidence for resource use then please provide details in appendix A.

See Clinical Commissioning Policy for Sacral Nerve Stimulation for Overactive Bladder

Reference: NHS England E10/P/b, July 2015
https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/10/e10pb-sacrl-nrve-stimltn-bladdr.pdf

and related NHS documentation.

Describe the resources needed to implement the technology in the NHS. Please provide sources and rationale.

The Axonics non-rechargeable SNM system would be used without any changes to clinical pathways or current practice of commissioned current SNM therapy for overactive bladder. Any training on the rechargeable SNM system is provided by Axonics at no charge to the NHS. As such, to our best judgment, we do not see a resource need to implement the technology in the NHS.

Describe the resources needed to manage the change in patient outcomes after implementing the technology. Please provide sources and rationale.

Per statements above, and clinical submission, no changes in therapy effectiveness are assumed. However, patients treated with rechargeable SNM therapy can expect a meaningful reduction in need for SNM device replacement and a potential reduction in need for device explantation on basis of improved MRI compatibility of the Axonics rechargeable device. These changes would result in benefits to patients, and hence will lower resource utilization in the NHS, i.e. lead to meaningful cost savings as quantified in the economic model.

Describe the resources needed to manage the change in system outcomes after implementing the technology. Please provide sources and rationale.

See statement above. No changes in system outcomes anticipated – other than patient-level cost savings and freed-up resources that would otherwise need to be available to manage the more frequent device replacements with non-rechargeable, as compared to rechargeable SNM therapy.

Table 5 Resource use costs

In this table, summarise how the model calculates the results of these changes in resource use. Please adapt the table as necessary.

	Technology costs	Comparator costs	Difference in resource use costs (technology vs comparator)
Cost of resource use to implement technology	0 (no additional costs, as SNM therapy already implemented in NHS)	0 (no additional costs, as SNM therapy already implemented in NHS)	0
Cost of resource use associated with patient outcomes	£21,223 (as projected by the model, over 15-year horizon; out of these, £15,289 device/materials cost)	£27,261 (as projected by the model, over 15-year horizon; out of these, £20,214 device/materials cost)	-£6,038 (out of these, -£4,925 device/materials cost)
Cost of resource use associated with system outcomes	0 (no additional costs considered, as any embedded in patient resource use above)	0 (no additional costs considered, as any embedded in patient resource use above)	0
Total costs	£21,223 (15-year analysis horizon)	£27,261 (15-year analysis horizon)	-£6,038 (15-year analysis horizon)

Adverse event costs

If costs of adverse events were included in the analysis, explain how and why the risk of each adverse event was calculated.

Adverse events were included in the analysis. Their frequencies were obtained from those studies providing the most contemporary data with sufficiently large sample size.

For surgical site infection, data from Brueseke et al, 2015 were used, a retrospective cohort analysis of 290 patients undergoing a total of 669 SNM procedures between 2002 and 2012 by 2 fellowship-trained female pelvic medicine and reconstructive surgery attending physicians at the University of California–Irvine Medical Center.

For surgical site pain, data from the InSite study were used (Noblett et al, 2016 – with additional data from that study shared by the study PI Dr. Karen Noblett)

For lead migration/dislodgment, data from the InSite study were used (Noblett et al, 2016 – with additional data from that study shared by the study PI Dr. Karen Noblett)

For lead fracture, data from the InSite study were used (Noblett et al, 2016 – with additional data from that study shared by the study PI Dr. Karen Noblett)

All of these adverse events were incorporated because they lead to resource utilization/costs. We note that our base case does not assume differences between the event rates of rechargeable and non-rechargeable devices, except accounting for a higher frequency of device replacements in the comparator, non-rechargeable technology – which leads to a total higher amount of adverse events related to replacement.

Table 6 Adverse events and costs in the model

In this table, summarise the costs associated with each adverse event included in the model. Include all adverse events and complication costs, both during and after long-term use of the technology. Please explain whether costs are provided per patient or per event.

Adverse event	Items	Cost	Source
Implant site infection requiring device replacement (costs are per event)	Technology	[redacted] (InterStim); £10,160 (Axonics)	Whole system, per current NHS Supply Chain cost (excl. VAT)
	Staff	0	Assumed to be included in reference costs
	Hospital costs	£3,531	Reference cost for LB79Z
	Total	[redacted] (InterStim); £13,691 (Axonics)	Sum of items above
Implant site infection requiring i.v. antibiotics treatment (costs are per event)	Technology	0	No device is assumed to be replaced in this case
	Staff	0	Assumed to be included in reference costs
	Hospital costs	£5,232	Reference costs for HRG WH07B
	Drugs	0	Assumed to be included in reference costs
	Total	£5,232	Sum of items above
Surgical site pain requiring explantation (costs are per event)	Technology	0	N/A
	Staff	0	Assumed to be included in reference costs
	Hospital costs	£5,136	Reference cost for HRG AA54C
	Total	£5,136	Sum of items above
Surgical site pain requiring revision (full device replacement required) (costs are per event)	Technology	[redacted] (InterStim); £10,160 (Axonics)	Whole system, per current NHS Supply Chain cost (excl. VAT)
	Staff	0	Assumed to be included in reference costs
	Hospital costs	£3,531	Reference cost for LB79Z
	Total	[redacted] (InterStim); £13,691 (Axonics)	Sum of items above
Lead migration/ dislodgment (costs are per event)	Technology	[redacted] (InterStim); £2,575 (Axonics)	Lead and introducer/tined lead implant, per current NHS Supply Chain cost (excl. VAT)
	Staff	0	Assumed to be included in reference costs
	Hospital costs	£1,500	Reference cost for HRG LB80Z
	Total	[redacted] (InterStim); £4,075 (Axonics)	Sum of items above

Lead fracture (costs are per event)	Technology	[redacted] (InterStim); £2,575 (Axonics)	Lead and introducer/tined lead implant, per current NHS Supply Chain cost (excl. VAT)
	Staff	0	Assumed to be included in reference costs
	Hospital costs	£1,500	Reference cost for HRG LB80Z
	Total	[redacted] (InterStim); £4,075 (Axonics)	Sum of items above

Miscellaneous costs

Describe any additional costs or resource considerations that have not been included elsewhere (for example, PSS costs, and patient and carer costs). If none, please state.

None.

Are there any other opportunities for resource savings or redirection of resources that have not been possible to quantify?

The Axonics' SNM technology's full-body MRI compatibility might offer additional savings relative to the current base case calculation, on the grounds of a reduced need for device explants in patients requiring full-body MRI. [See also sensitivity analysis scenario performed to explore potential cost savings associated with MRI compatibility]

Total costs

In the following tables, summarise the total costs:

- Summarise total costs for the technology in table 7.
- Summarise total costs for the comparator in table 8. This can only be completed if the comparator is another technology.

Table 7 Total costs for the technology in the model

Description	Cost	Source
Cost per treatment/patient over analysis horizon (15 yrs. in base case)	£21,223	Economic model, base case, 15 yrs.
Consumables per year (if applicable) and over lifetime of device	Only incontinence pads were considered	N/A
Maintenance cost per year and over lifetime of device	No maintenance costs other than device replacement and AE management, which are included in cost per treatment/patient	N/A
Training cost over lifetime of device	0 (provided at no cost to NHS by the manufacturer)	Axonics Neuromodulation, Inc.
Other costs per year and over lifetime of device	Not applicable	N/A
Total cost per treatment/patient over analysis horizon (15 yrs. in base case)	**£21,223**	Sum of costs

Table 8 Total costs for the comparator in the model

Description	Cost	Source
Cost per treatment/patient over analysis horizon (15 yrs. in base case) [includes incontinence pad costs for patients who have discontinued therapy]	£27,261	Economic model, base case, 15 yrs.
Consumables per year (if applicable) and over lifetime of device	Not applicable	N/A
Maintenance cost per year and over lifetime of device	No maintenance costs other than device replacement and AE management, which are included in cost per treatment/patient	N/A
Training cost over lifetime of device	0 (provided at no cost to NHS by the manufacturer)	Current practice, per Axonics Neuromodulation Inc. information
Other costs per year and over lifetime of device	Not applicable	N/A
Total cost per treatment/patient over analysis horizon (15 yrs. in base case)	**£27,261**	Sum of costs

Results

Table 9 Base-case results

In this table, report the results of the base-case analysis. Specify whether costs are provided per treatment or per year. Adapt the table as necessary to suit the cost model. If appropriate, describe costs by health state.

	Mean discounted cost per patient using the technology (£) [15 yrs. horizon]	**Mean discounted cost per patient using the comparator (£) [15 yrs. horizon]**	**Difference in mean discounted cost per patient (£): technology vs comparator [15 yrs. horizon]**
Device cost (without AE-related device costs, which are shown in AE section)	14,707	19,679	-4,972
Training cost	0	0	0
Administration cost	5,295	6,286	-991
Monitoring costs	0	0	0
Consumables (incontinence pads for patients who discontinued SNM)	301	301	0
Adverse events	338 treatment costs +582 device costs	460 treatment costs +535 device costs	-75
Total	**21,223**	**27,261**	**-6,038**

Scenario analysis

If relevant, explain how scenario analyses were identified and done. Cross-reference your response to the decision problem in part 1, section 1 of the submission.

As the primary differentiator between rechargeable and non-rechargeable SNM is the lifetime of the devices before they need to be replaced, understanding the effect of changes in the analysis horizon is important (aside from sensitivity analyses of each technologies' lifetime, which are performed as part of sensitivity analyses).

We performed three alternative scenario analyses, complementing the 15-year base case. These include a 10-year, 20-year, and 25-year analysis horizon.

Describe the differences between the base case and each scenario analysis.

The difference between each of the analysis horizon scenarios and the base case is the time the model follows the cohort to calculate cost difference.

While the cost comparison is most appropriately conducted for patients receiving SNM therapy, we also ran a scenario analysis that included the testing conducted prior to definitive implantation of SNM. No differences were assumed between the testing response rates of patients in the rechargeable and non-rechargeable strategies of this scenario analysis. Testing parameters are included in the model inputs and referenced there. Note that in this scenario analysis, only 66% of patients receive full system implantation. As such, savings associated with rechargeable strategy will be somewhat lower, if this different cohort is evaluated.

Describe how the scenario analyses were included in the cost analysis.

The analysis horizon scenarios were included in the cost analysis by evaluating the difference in cumulative costs at the shorter time horizon (10yrs.), or at the longer time horizons (20, 25 and 30 yrs.). No other changes were made to the model, other than continuing the Markov traces/calculations.

The scenario that considers the different cohort (patients undergoing evaluation for response to SNM) uses a decision tree analysis that models the testing procedures and testing outcomes, and tracks their costs. The subsequent cost of actual SNM therapy is then modelled and accounted for in the percent of patients who are implanted with SNM systems, based on their response. [Note: to run this scenario analysis, select choice field in cell B9 in "Results-Cost" tab, and select "Tested and treated cohort" instead of "treated cohort only (without test)"

Describe the evidence that justifies including any scenario analyses.

SNM therapy for OAB is intended as a long-term therapy. At assumed mean cohort age of 57 yrs., the 15-year horizon projects to 73 yrs. of age, while the 20, 25, and 30-year horizons project to 78, 83, and 88 yrs., respectively, reaching follow-up horizons commensurate with the life expectancy of the cohort.

The scenario analysis that evaluates a different cohort (those referred to for evaluation of SNM) was included for completeness only.

Table 10 Scenario analyses results

In this table, describe the results of any scenario analyse that were done. Adapt the table as necessary.

	Mean discounted cost per patient using the technology (£)	Mean discounted cost per patient using the comparator (£)	Difference in cost per patient (£)*
10-year analysis horizon (total costs)	16,619	23,144	-6,525

20-year analysis horizon (total costs)	21,540	30,281	-8,742
25-year analysis horizon (total costs)	22,088	32,549	-10,461
30-year analysis horizon (total costs)	23,433	34,143	-10,710
Analysis of patients receiving test evaluation, followed by subsequent SNM treatment only in responders (NOTE: different cohort/decision question!) (Total budget impact, and hence cost savings to NHS of rechargeable vs. non-rechargeable SNM use can be expected to be the same as those based on the base case analysis, as the slightly lower cost savings in this scenario analysis apply to a larger population (those undergoing testing) than those evaluated in the base case (those receiving SNM after positive test).	£17,708	£21,604	-£3,896
* Negative values indicate a cost saving. Adapt this table as necessary.			

Sensitivity analysis

Describe what kinds of sensitivity analyses were done. If no sensitivity analyses have been done, please explain why.

Comprehensive one-way sensitivity analyses were performed varying the clinical input parameters and device parameters across the ranges specified previously (Table 3).

Two-way sensitivity analyses were done to explore potential variations of device lifetime of the rechargeable and non-rechargeable systems.

Summarise the variables used in the sensitivity analyses and provide a justification for them. This may be easier to present in a table (adapt as necessary).

All relevant cohort and technical parameters were varied according to input ranges stated in Table 3.

Justification for each: need to understand effect on cost difference for variation of each parameter.

Patient age
Therapy discontinuation, first year
Therapy discontinuation, 2nd and following years
Implant site infection, index procedure
Implant site infection, replacement procedures
Surgical site pain requiring surgical intervention
Lead migration/dislodgment
Lead fracture

Required stimulator replacement, non-rechargeable
Required stimulator replacement, rechargeable
Programming visits, first year
Programming visits, second year

If any parameters or variables listed in table 3 were omitted from the sensitivity analysis, please explain why.

None were omitted.

Sensitivity analyses results

Present the results of any sensitivity analyses using tornado plots when appropriate.

One-way sensitivity analyses:

SCENARIO	Cost Rechargeable	Cost Non-rechargeable	Cost difference
Base case	£ 21,223	£ 27,261	-£ 6,038
Patient age 43 yrs.	£ 21,734	£ 27,892	-£ 6,158
Patient age 71 yrs.	£ 19,292	£ 24,835	-£ 5,543
Therapy discontinuation, first year, per 3-month cycle 0.56%	£ 21,155	£ 27,426	-£ 6,271
Therapy discontinuation, first year, per 3-month cycle 3.36%	£ 21,446	£ 26,722	-£ 5,276
Therapy discontinuation, 2nd and following years, per 3-month cycle 0.05%	£ 21,218	£ 27,290	-£ 6,073
Therapy discontinuation, 2nd and following years, per 3-month cycle 0.30%	£ 21,266	£ 27,012	-£ 5,745
Implant site infection, index procedure 2.2%	£ 21,042	£ 27,008	-£ 5,966
Implant site infection, index procedure 19.1%	£ 22,381	£ 28,878	-£ 6,497
Implant site infection, replacement procedure 1.1%	£ 21,188	£ 27,136	-£ 5,948
Implant site infection, replacement procedure 9.55%	£ 21,445	£ 28,059	-£ 6,615

Surgical site pain requiring surgical intervention 2%	£ 20,991	£ 27,051	-£ 6,061
Surgical site pain requiring surgical intervention 10%	£ 21,900	£ 27,871	-£ 5,971
Lead migration/dislodgment 0.55%	£ 21,200	£ 27,242	-£ 6,042
Lead migration/dislodgment 2.20%	£ 21,268	£ 27,297	-£ 6,029
Lead fracture 0.5%	£ 21,183	£ 27,229	-£ 6,045
Lead fracture 5.0%	£ 21,367	£ 27,376	-£ 6,010
Required stimulator replacement, non-rechargeable, 2.0 yrs.	£ 21,223	£ 46,037	-£24,814
Required stimulator replacement, non-rechargeable, 7.0 yrs.	£21,223	£22,279	-£1,056
Required stimulator replacement, rechargeable, 10.8 yrs.	£22,300	£27,261	-£4,961
Required stimulator replacement, rechargeable, 19.2 yrs.	£17,515	£27,261	-£9,746
Programming visits first year 1.0	£21,103	£27,140	-£6,038
Programming visits first year 3.0	£21,314	£27,351	-£6,038
Programming visits subsequent years 1.0	£21,497	£27,535	-£6,038
Programming visits subsequent years 3.0	£23,607	£29,645	-£6,038

Two-way sensitivity analyses on device lifetime (only showing cost difference), 15-year horizon:

	Rechargeable 10.8 yrs.*	Rechargeable 15.0 yrs.	Rechargeable 19.2 yrs.
Non-rechargeable 2.0 yrs.	-£23,964	-£24,814	-£28,522
Non-rechargeable 4.4 yrs.	-£5,188	-£6,038	-£9,746
Non-rechargeable 7.0 yrs.	-£206	-£1,056	-£4,764

as mentioned in inputs, the rechargeable lifetime of 10.8 yrs. is a **hypothetical scenario, tested only for exploratory purposes. The expected computed average lifetime of the rechargeable device is 19.2 yrs. It is approved based on a lifetime of at least 15 years, the value assumed for the economic base case.*

Use of 208-19 tariffs instead of reference costs:

	Cost Rechargeable	**Cost Non-rechargeable**	**Cost difference**
Tariff-based costs	£19,855	£25,752	-£5,897

What were the main findings of each of the sensitivity analyses?

The main findings of the sensitivity analyses are that

- Rechargeable SNM therapy, compared to non-rechargeable was cost saving across all tested scenarios
- Parameters that affect both strategies similarly have no or only minimal impact on the cost difference, as would be expected
- Use of tariff instead of reference costs reduces projected savings minimally

What are the main sources of uncertainty about the model's conclusions?

The main sources of variation in amount of cost savings of rechargeable SNM therapy were the device lifetimes of each of the devices. However, varying these parameters about a very wide range of assumptions does not change the conclusion that rechargeable SNM therapy will be associated with cost savings to the NHS.

Note that variations in cost, other than use of tariff instead of reference costs, were not explored, as the procedure costs are well established, and the device costs are published NHS Supply Chain costs. If further analyses are desirable, they can readily be conducted using the submitted economic model.

Miscellaneous results

Include any other relevant results here.

As mentioned in the clinical submission, the Axonics rechargeable SNM device is fully MRI compatible up to 3 Tesla, while the non-rechargeable InterStim is not. To stay conservative, the base case does not account for potential differences in the need for temporary or permanent device explants that might be performed in the NHS.

Any such explantations performed because of MRI incompatibility would be associated with explant-associated risk and discomfort to the patient, but also NHS resource use – and if a device is reimplanted – additional device costs. An explantation without replacement would incur costs of at least £2,379 (HRG AA54C), while eventual reimplantation would require additional reimplantation costs of at least £672 (HRG AA57A) plus device costs of £5,872.

Validation

Describe the methods used to validate, cross-validate (for example with external evidence sources) and quality assure the model. Provide sources and cross-reference to evidence when appropriate.

Throughout the original model development (Noblett et al, 2017), three clinical experts were closely involved to validate the clinical assumptions and overall structure of the health-economic model.

Technical validation:
Multiple validation checks were performed, with the most important checks listed below:

Patient survival: Survival projections ('cohort alive') at 15 years were compared to survival computed directly from underlying 2015-17 lifetables for England to confirm proper calculation in the model.
Device replacement events: Checks were performed to ensure device lifetime entered in inputs leads to corresponding replacement event in the correct cycle(s) of the model, and corresponding costs incurred.
Cumulative therapy discontinuation events were compared to the inputs, and inputs compared to the original sources (see input tables for references) to ensure accuracy in (cumulative) projection of therapy discontinuation.

For quality assurance, the model implementation was internally cross-checked by a second programmer/analyst.

Give details of any clinical experts who were involved in validating the model, including names and contact details. Highlight any personal information as confidential.

The clinical co-authors of the original publication (Noblett et al, 2017) were closely involved in validating the original United States model and confirming the appropriateness of its assumptions. Of note, Dr. Noblett also was one of the principal investigators of the Insite study, the largest SNM study which also comprehensively evaluated adverse events.

Contact information (CONFIDENTIAL):

[redacted]

For the context of the UK analysis, we referred to the specialist comments included in the recent Axonics Medtech innovation briefing [MIB164] (published date: December 2018 – https://www.nice.org.uk/advice/mib164). The following UK clinicians contributed to that NICE briefing:

- Dermot Burke, associate professor of clinical surgery, St James's Hospital, Leeds, did not declare any interests.
- Mahreen Pakzad, consultant urological surgeon, University College London Hospitals (UCLH), non-financial professional actively involved in 2 ongoing clinical trials involving the Axonics sacral neuromodulation (SNM) system and 1 ongoing trial involving the Medtronic SNM system.
- Andrew Thorpe, consultant urologist, Newcastle upon Tyne Hospitals NHS Foundation Trust, departmental fellowships received from Medtronic from October 2018 to February 2019.
- Karen Nugent, senior lecturer, University of Southampton, Association of Coloproctology (Great Britain and Ireland), did not declare any interests.
- Jane Brocksom, senior urology clinical nurse specialist, Leeds Teaching Hospital NHS Trust, British Association of Urological Nurses (BAUN), did not declare any interests.
- Julie Jenks, advanced nurse practitioner, University College London Hospitals (UCLH), paid consultant for Medtronic; position expired end of October 2018.
- Christopher Harding, consultant urological surgeon, Newcastle upon Tyne Hospitals NHS Foundation Trust, British Association of Urological Surgeons (Chairman of Female, Neurological and Urodynamic Urology Subsection), paid speaker fees from Medtronic and Department of Urology, Newcastle upon Tyne Hospitals NHS Foundation Trust received proctoring fees and an educational grant from Medtronic.

As the comments provided by the specialists were directly in line with the prior clinical experts' opinion, no need was seen to involve further specialist input from the UK for the purposes of this economic model.

Of note, the main economic benefit was confirmed by the UK specialists: *"Most of the commentators thought the longer battery life would provide the largest benefit to patients, and that using the new technology would lead to fewer revision surgeries."*

4 Summary and interpretation of economic evidence

Describe the main findings from the economic evidence and cost model. Explain any potential cost savings and the reasons for them.

Our main finding is that the longer lifetime of the rechargeable Axonics SNM technology, compared to other, non-rechargeable SNM technology, can be expected to lead to substantial savings to the UK NHS. These savings result predominantly from fewer required device replacements, but also from lower adverse event costs associated with replacement procedures.

Briefly discuss the relevance of the evidence base to the scope.

The economic evidence, in conjunction with the provided clinical evidence, is central in answering the assessment question defined in the scope. Appreciation of the nature and amount of the projected savings is critical information for decision making by the NHS.

Briefly discuss if the results are consistent with the published literature. If they are not, explain why and justify why the results in the submission be favoured over those in the published literature.

Given the relative novelty of the Axonics SNM system, only one prior study (Noblett et al, 2017) has compared to costs of a rechargeable vs. non-rechargeable SNM strategy for treatment of OAB. The findings of the current study for the UK NHS perspective are in line with the Noblett et al. study, which was performed in the context of the United States healthcare system.

Of note, the cost-saving potential of rechargeable neurostimulation therapy has previously been assessed and confirmed, albeit in other clinical indication areas. For example, Hornberger et al, Clin J Pain. 2008 Mar-Apr;24(3):244-52 – which found rechargeable vs. non-rechargeable spinal cord stimulation technology for patients with failed back surgery syndrome to save up to $100,000 over a patient's lifetime.

Describe if the cost analysis is relevant to all patient groups and NHS settings in England that could potentially use the technology as identified in the scope.

Yes, the cost analysis is relevant to all patient groups and NHS settings. As shown in sensitivity analyses, the absolute amount of cost savings may differ somewhat between different patient groups, and might differ somewhat based on local NHS cost information, if they differ from the reference costs used in the base case analysis. However, none of these factors can be expected to lead to saving amounts that would not be meaningful to the NHS.

Briefly summarise the strengths and limitations of the cost analysis, and how these might affect the results.

The strength of the current cost model is that it provides a detailed projection of all relevant events and costs incurred, with consideration of patient survival to properly calculate long-term savings.

Limitations include scarce data about long-term discontinuation of therapy, as published evidence is limited to five years of follow-up. However, these discontinuation rates would apply to both Axonics and the non-rechargeable comparator. As shown in sensitivity analyses, the effect of variation in this parameter would not lead to material changes of the results. Further, clinical evidence about the additional benefits associated with the MRI-compatibility of the Axonics system is limited. Although data on the need for MRI in the general population is available in national databases (see OECD database https://data.oecd.org/healthcare/magnetic-resonance-imaging-mri-exams.htm), specific data on need for MRI in the SNM population are limited. Availability of such data would help to corroborate the additional benefit of the MRI-compatible the Axonics technology, which is not included in the current base case calculations. As such, the current base case likely underestimates associated savings somewhat.

Detail any further analyses that could be done to improve the reliability of the results.

Device lifetimes are the most important factor influencing the calculated cost difference. As such, any current UK NHS-specific information about the comparator's lifetime would be useful to corroborate the current assumptions. However, we do not expect such data to deviate meaningfully from previously published and manufacturer-provided data. In addition, as has been shown through sensitivity analysis, even markedly longer assumed lifetime of the non-rechargeable comparator technology would not alter the overall finding of substantial cost savings associated with the rechargeable technology.

In addition, further research into detailed costs of treatment of device infection requiring i.v. antibiotic treatment in the NHS setting would be useful to further inform and confirm the current model input for this cost. However, as has been shown in the analyses, additional detail, again, would not be expected to meaningfully affect the current cost projections and computed savings.

5 References

Please include all references below using NICE's standard referencing style.

Arlandis S, Castro D, Errando C, et al. (2011) Cost-effectiveness of sacral neuromodulation compared to botulinum neurotoxin a or continued medical management in refractory overactive bladder. Value in Health 14 (2): 219-228

Bertapelle MP, Vottero M, Popolo GD, et al. (2015) Sacral neuromodulation and Botulinum toxin A for refractory idiopathic overactive bladder: a cost-utility analysis in the perspective of Italian Healthcare System. World journal of urology 33 (8): 1109-1117

Brueseke T, Livingston B, Warda H, et al. (2015) Risk Factors for Surgical Site Infection in Patients Undergoing Sacral Nerve Modulation Therapy. Female Pelvic Med Reconstr Surg 21 (4): 198-204

Cameron AP, Anger JT, Madison R, et al. (2013) Battery explantation after sacral neuromodulation in the Medicare population. Neurourol Urodyn 32 (3): 238-241

Chughtai B, Clemens JQ, Thomas D, et al. (2019) Real World Performance of SNM and OnabotulinumtoxinA for OAB: Focus on Safety and Cost. The Journal of urology: 101097JU0000000000000462

Chughtai B, Sedrakyan A, Isaacs A, et al. (2015) Long term safety of sacral nerve modulation in medicare beneficiaries. Neurourol Urodyn 34 (7): 659-663

Freemantle N, Khalaf K, Loveman C, et al. (2016) OnabotulinumtoxinA in the treatment of overactive bladder: a cost-effectiveness analysis versus best supportive care in England and Wales. European Journal of Health Economics 17 (7): 911-921

Hassouna MM, & Sadri H Economic evaluation of sacral neuromodulation in overactive bladder: A Canadian perspective. Canadian Urological Association journal = Journal de l'Association des urologues du Canada 9 (7-8): 242-247

Hornberger J, Kumar K, Verhulst E, et al. (2008) Rechargeable spinal cord stimulation versus non-rechargeable system for patients with failed back surgery syndrome: a cost-consequences analysis. Clin J Pain 24 (3): 244-252

Kantartzis KL, & Shepherd JP (2013) Cost-effectiveness of test phase implantation strategies for interstim® sacral neuromodulation. Female Pelvic Medicine and Reconstructive Surgery 19 (6): 322-327

Leong RK, De Wachter SGG, Joore MA, et al. (2011) Cost-effectiveness analysis of sacral neuromodulation and botulinum toxin A treatment for patients with idiopathic overactive bladder. BJU International 108 (4): 558-564

Leroi AM, Lenne X, Dervaux B, et al. (2011) Outcome and cost analysis of sacral nerve modulation for treating urinary and/or fecal incontinence. Annals of Surgery 253 (4): 720-732

Martinson M, MacDiarmid S, & Black E (2013) Cost of neuromodulation therapies for overactive bladder: Percutaneous tibial nerve stimulation versus sacral nerve stimulation. Journal of Urology 189 (1): 210-216

Medical Advisory Secretariat (2005) Sacral nerve stimulation for urinary urge incontinence, urgency-frequency, urinary retention, and fecal incontinence: an evidence-based analysis. Toronto: Medical Advisory Secretariat Ontario Ministry of Health and Long-Term Care (MAS) Medical Advisory Secretariat (MAS)

Murray B, Hessami SH, Gultyaev D, et al. (2019) Cost-effectiveness of overactive bladder treatments: From the US payer perspective. Journal of Comparative Effectiveness Research 8 (1): 61-71

Nikolavsky D, Killinger K, Boura J, et al. (2011) Comparison of patients undergoing a two-stage sacral nerve stimulation procedure: Is there a cost benefit for a single-stage procedure? International Urology and Nephrology 43 (4): 997-1002

Noblett K, Siegel S, Mangel J, et al. (2016) Results of a prospective, multicenter study evaluating quality of life, safety, and efficacy of sacral neuromodulation at twelve months in subjects with symptoms of overactive bladder. Neurourol Urodyn 35 (2): 246-251

Noblett KL, Dmochowski RR, Vasavada SP, et al. (2017) Cost profiles and budget impact of rechargeable versus non-rechargeable sacral neuromodulation devices in the treatment of overactive bladder syndrome. Neurourology and Urodynamics 36 (3): 727-733

Patel DN, Zhao HH, Houman J, et al. (2019) Comparative effectiveness of one versus two-stage sacral neurostimulation device placement. Neurourology and Urodynamics 38 (2): 734-739

Siddiqui NY, Amundsen CL, Visco AG, et al. (2009) Cost-Effectiveness of Sacral Neuromodulation Versus Intravesical Botulinum A Toxin for Treatment of Refractory Urge Incontinence. Journal of Urology 182 (6): 2799-2804

Sun AJ, Harris CR, Comiter CV, et al. (2019) To stage or not to stage?—A cost minimization analysis of sacral neuromodulation placement strategies. Neurourology and Urodynamics 38 (6): 1783-1791

Watanabe JH, Campbell JD, Ravelo A, et al. (2010) Cost analysis of interventions for antimuscarinic refractory patients with overactive bladder. Urology 76 (4): 835-840

Wielage RC, Perk S, Campbell NL, et al. (2016) Mirabegron for the treatment of overactive bladder: cost-effectiveness from US commercial health-plan and Medicare Advantage perspectives. Journal of Medical Economics 19 (12): 1135-1143

Yehoshua A, Murray BP, Vasavada SP, et al. (2018) Comparing direct medical costs of onabotulinumtoxina with other common overactive bladder interventions. American Journal of Pharmacy Benefits 10 (1): 11-17

6 Appendices

Appendix A: Search strategy for economic evidence

Describe the process and methods used to identify and select the studies relevant to the technology being evaluated. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	August 22, 2019
Date span of search:	2010 to 2019
List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	

Sources: The search for economic evaluations was performed in August 2019, using a combination of searches in Embase, Medline/Pre-Medline, Health Technology Assessment Database, and NHS Economic Evaluation Database (see below for details).

Search Strategy: We combined the clinical search terms (overactive bladder/urge/urge incontinence – no search terms for other incontinence types, but exclusion in the full text review) with ones for economic evaluations (building on previous, similar searches). The search strategies were individualized for each database and are detailed below. The inclusion and exclusion criteria are listed below. We only made use of a small number of filters in PubMed/Medline as to keep the initial search relatively broad. Review and papers that only reported the design of a study (but no results) were used to search for other relevant papers.

EMBASE SEARCH

- **Database:** Embase Classic+Embase 1967 (plus <1966) to August 2019
- **Limits:** none
- **Search Date:** August 22, 2019
- **Search Terms and Strategy:**

#	Searches	Results
1	'health economics'/exp OR 'health economics' OR 'economic evaluation' OR 'health care cost' OR pharmacoeconomics OR econom* OR pharmacoeconomic* OR 'cost effectiveness analysis' OR 'cost utility analysis' OR 'cost minimization analysis' OR 'cost benefit analysis' OR ('cost benefit' AND analysis) OR (budget AND impact AND analysis) OR 'cost effective*'	1,451,265
2	'overactive bladder'	16,780
3	'urge incontinence'	7,888
4	urgency AND incontinence	9,680
5	'urinary urgency'	6,870
6	urge AND 'incontinence'	9,451
7	#2 OR #3 OR #4 OR #5 OR #6	30,373
8	#1 AND #7	1,810
9	(bladder* (overactiv* or over activ* or over-activ* or instabilit* or hyper-reflex* or hyperreflex* or hyper reflex* or incontinen*))	36,967

10	detrusor* AND ((overactiv* OR over) AND activ* OR 'over activ*' OR instabilit* OR 'hyper reflex*' OR hyperreflex* OR hyper) AND reflex*	7,511
11	#7 OR #9 OR #10	53,738
12	#1 AND #11	2,483
13	'neuromodulation'	48,260
14	'sacral nerve stimulation'	2,965
15	'sacral nerve stimulator'	210
16	sacral AND neuro AND modulation	36
17	sacral AND neuro AND modulator	0
18	sacral AND neuro AND stimulation	172
19	sacral AND neuro AND stimulator	25
20	sacral AND modulation	401
21	sacral AND modulator	17
22	sacral AND stimulation	5,012
23	sacral AND stimulator	792
24	neuro AND modulation	3,545
25	neuro AND modulator	503
26	neuro AND stimulation	9,905
27	neuro AND stimulator	437
28	nerve AND modulation	45,550
29	nerve AND modulator	4,842
30	nerve AND stimulation	195,693
31	nerve AND stimulator	8,803
32	'devices'	660,446
33	'medical device'	58670
34	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32	948,542
35	#11 AND #34	5,673
36	#1 AND #35	437

MEDLINE SEARCH

- **Databases:** PubMed/Medline/Pre-Medline 1946 to August 2019
- **Limits/Filters**:
  - Publication type: NOT letter, editorial, or historical article
  - Species: not animal or mixed study
- **Search Date:** August 22, 2019
- **Search Terms and Strategy:**

#	Searches	Results
1	"Economics"[Mesh:NoExp] OR "Costs and Cost Analysis"[Mesh] OR "Economics, Hospital"[Mesh] OR "Economics, Medical"[Mesh:NoExp] OR "Economics, Nursing"[Mesh] OR "Economics, Pharmaceutical"[Mesh] OR economic*[tiab] or cost[tiab] or costs[tiab] or costly[tiab] or costing[tiab] or price[tiab] or prices[tiab] or pricing[tiab] or pharmacoeconomic*[tiab] OR (expenditure*[tiab] not energy[tiab]) OR "value for money"[tiab] OR budget*[tiab] NOT ("energy cost"[Title/Abstract] OR "oxygen cost"[tiab] OR "metabolic cost"[tiab] OR energy expenditure[tiab] OR "oxygen expenditure"[tiab] OR (letter[pt] OR editorial[pt] OR historical article[pt]) OR animals[mesh:noexp])	766,040
2	"Urinary Incontinence, Urge"[Mesh]	875

3	"Urinary Bladder, Overactive"[Mesh]	4,269
4	"Urinary Bladder"[Mesh] OR "urinary"[tiab] OR "urine"[tiab] "bladder"[tiab] OR void*[tiab]	105,951
5	"urge"[tiab] OR "urgency"[tiab]	23,301
6	"Urinary Incontinence"[Mesh] OR "Urinary Incontinence"[tiab] OR "incontinence"[tiab] OR "incontinent*"[tiab]	55,319
7	#4 AND #5	4,898
8	#5 AND #6	6,609
9	"detrusor"[tiab] AND ("over active"[tiab] OR "over activity"[tiab] OR "over-active"[tiab] OR "over-activity"[tiab] OR "overactive"[tiab] OR "overactivity"[tiab] OR contract*[tiab] OR uninhibit*[tiab] OR involuntary*[tiab])	5,852
10	#2 OR #3 OR #7 OR #8 OR #9	14,991
11	#1 AND #10	514
12	"Implantable Neurostimulators"[MeSH]	10,499
13	sacrum[tiab] or sacral[tiab]	19,932
14	nerve[tiab] OR neurost*[tiab] OR neuromo*[tiab] OR stimulat*[tiab] OR modulat*[tiab]	1,949,416
15	#13 AND #14	4,784
16	"Prostheses and Implants"[MeSH]	496,695
17	"Electrodes, Implanted"[MeSH]	44,006
18	"Implants, Experimental"[MeSH]	3,251
19	device*[tiab]	387,161
20	implant*[tiab]	381,279
21	#16 OR #17 OR #18 OR #19 OR #20	1,039,122
22	#15 OR #21	1,042,612
23	#10 AND #22	1,781
24	#1 AND #23	101

HEALTH TECHNOLOGY ASSESSMENT DATABASE SEARCH

- **Database:** University of York, Centre for Reviews and Dissemination, Health Technology Assessment Database
- **Limits:** none
- **Search Date:** August 22, 2019
- **Search Terms and Strategy:**

#	Searches	Results
1	MeSH descriptor: [Urinary Incontinence] this term only	0
2	MeSH descriptor: [Urinary Incontinence, Urge] this term only	51
3	MeSH descriptor: [Urinary Bladder, Overactive] this term only	10
4	(bladder*):TI OR (detrusor*):TI OR (urin*):TI	201
5	(urge*):TI OR (incont*):TI	131
6	(overact*):TI OR (over-act*):TI OR (over act*):TI	12
7	(hyperreflex*):TI OR (hyper-reflex*):TI OR (hyper reflex*):TI	0
8	(contract*):TI OR (uninhibit*):TI OR (involuntary*):TI	23
9	#1 OR #2 OR #3	58
10	#4 AND #5	71
11	#4 AND #6	2
12	#4 AND #7	0
13	#4 AND #8	0
14	#5 AND #6	2

15	#5 AND #7	0
16	#5 AND #8	0
17	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	90
18	MeSH descriptor: ["Implantable Neurostimulators"] this term only	0
19	MeSH descriptor: ["Prostheses and Implants"] this term only	0
20	MeSH descriptor: ["Electrodes, Implanted"] this term only	0
21	MeSH descriptor: ["Implants, Experimental"] this term only	0
22	(sacrum):TI OR (scaral):TI	0
23	(nerve*):TI OR (neuro*):TI	337
24	(stimulat*):TI OR (modulat*):TI	283
25	(neurostimulat*):TI OR (neuromodulat*):TI	24
26	(device*):TI OR (implant*):TI	564
27	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	1,080
28	#17 AND #27	21

NHS ECONOMIC EVALUATION SEARCH

- **Database:** University of York, Centre for Reviews and Dissemination, NHS Economic Evaluation (NHS EE) Database
- **Limits:** none
- **Search Date:** August 22, 2019
- **Search Terms and Strategy:**

#	Searches	Results
1	MeSH descriptor: [Urinary Incontinence] this term only	31
2	MeSH descriptor: [Urinary Incontinence, Urge] this term only	6
3	MeSH descriptor: [Urinary Bladder, Overactive] this term only	27
4	(bladder*):TI OR (detrusor*):TI OR (urin*):TI	198
5	(urge*):TI OR (incont*):TI	64
6	(overact*):TI OR (over-act*):TI OR (over act*):TI	32
7	(hyperreflex*):TI OR (hyper-reflex*):TI OR (hyper reflex*):TI	0
8	(contract*):TI OR (uninhibit*):TI OR (involuntary*):TI	13
9	#1 OR #2 OR #3	59
10	#4 AND #5	33
11	#4 AND #6	32
12	#4 AND #7	0
13	#4 AND #8	0
14	#5 AND #6	2
15	#5 AND #7	0
16	#5 AND #8	0
17	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	80
18	MeSH descriptor: ["Implantable Neurostimulators"] this term only	0
19	MeSH descriptor: ["Prostheses and Implants"] this term only	0
20	MeSH descriptor: ["Electrodes, Implanted"] this term only	0
21	MeSH descriptor: ["Implants, Experimental"] this term only	0
22	(sacrum):TI OR (scaral):TI	0
23	(nerve*):TI OR (neuro*):TI	155
24	(stimulat*):TI OR (modulat*):TI	153
25	(neurostimulat*):TI OR (neuromodulat*):TI	10
26	(device*):TI OR (implant*):TI	289
27	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	571
28	#17 AND #27	16

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):
n.a.
Inclusion and exclusion criteria:

Inclusion criteria:
• English-language full-text publications
• Studies published between 2000 up until August 22, 2019
• Studies in patients with overactive bladder, defined as urge or urge incontinence, for whom pharmaceutical treatment was not effective or not effective enough or who were not candidates for those
• Studies reporting on sacral neuromodulation
• Some form of comparator, e.g., another neuromodulation implantable device
• Economic evaluations:
  ○ Cost-utility analyses (CUAs)
  ○ Cost-effectiveness analyses (CEAs) with an effectiveness measure other than utility
  ○ Cost-benefit analyses (CBAs)
  ○ Budget impact analyses
  ○ Cost minimization analyses (CMA)
 	
Exclusion criteria:
• Studies that only included patients with stress or overflow incontinence
• Abstracts/conference proceedings who were not subsequently published as a full text
• Commentary/editorials/opinion pieces
• Letters including research
• Review articles, including systematic reviews
• Papers that only described a study design but did not report results
• Studies that reported only on resource use or cost components but not the full treatment

Data abstraction strategy:
The data were directly abstracted into the fields suggested by the NICE Company Evidence Submission template.

Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

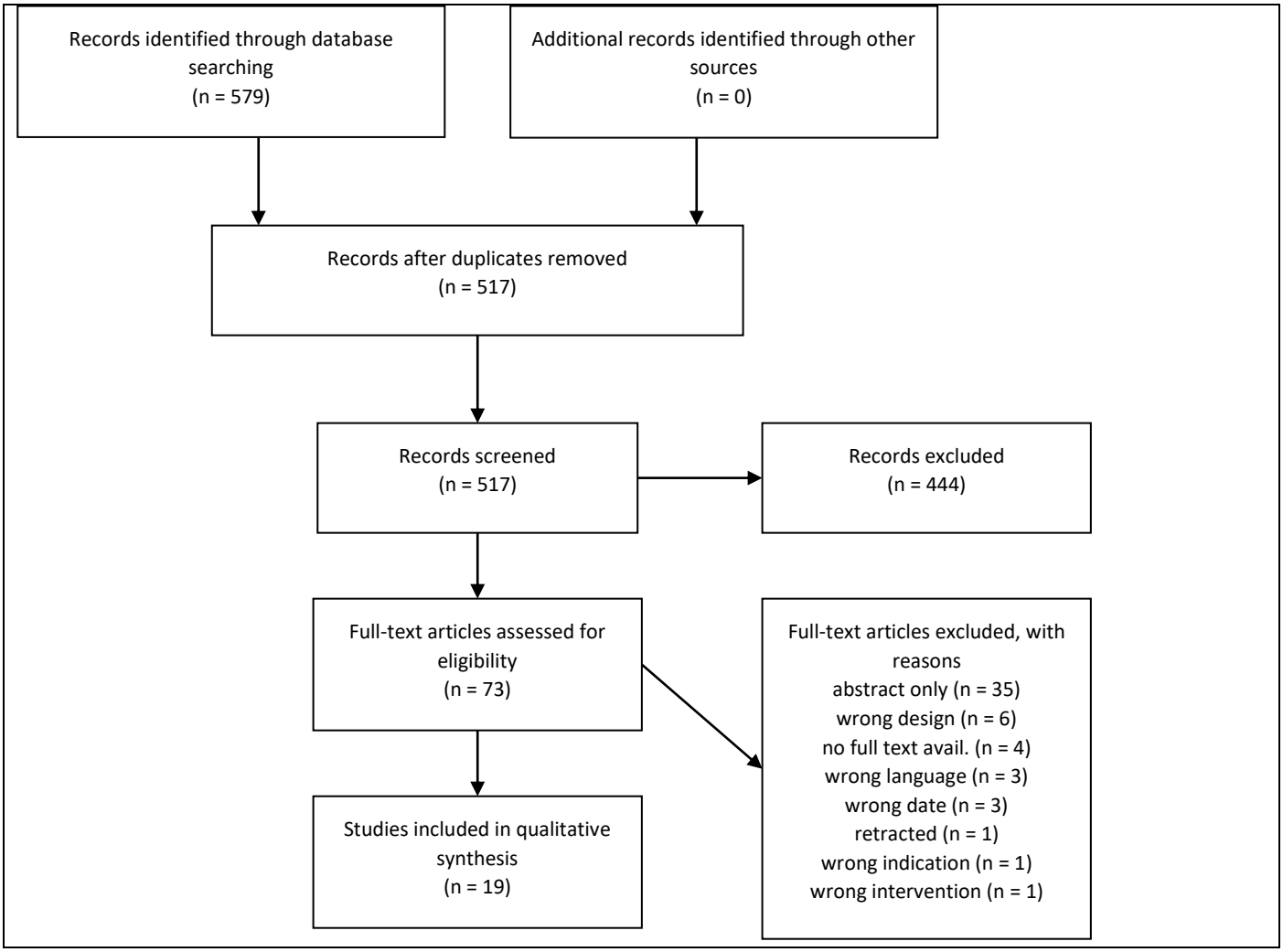
Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
Almazan 2002	HTA; sacral neuromodulation	Wrong language	Spanish language
Almazan 2000	HTA; sacral neuromodulation	Wrong language	Spanish language
Anger 2014	CEA; sacral neuromodulation	Wrong study design	Study investigated the effect on anticholinergic costs
Arlandis 2009a	CEA; sacral neuromodulation, botulinum neurotoxin, and optimized medical treatment	Abstract only	
Arlandis 2009b	CEA; sacral neuromodulation, botulinum neurotoxin, and optimized medical treatment	Abstract only	
Autiero 2015	CEA; sacral neuromodulation	Retracted	The paper was retracted due to unreconcilable errors in the model design
Bertapelle 2013	CEA; sacral neuromodulation, botulinum neurotoxin	Abstract only	
Borisenko 2015	CEA; sacral neuromodulation, botulinum neurotoxin	Abstract only	
Canadian Coordinating Office for Health Technology Assessment 2002	HTA; sacral neuromodulation	Wrong study design	No economic evaluation
Castaño 2014	CEA; sacral neuromodulation, botulinum neurotoxin	Abstract only	
Castro Díaz 2011	Budget impact analysis; sacral neuromodulation	Abstract only	
Clemens 2011	CEA; sacral neuromodulation, botulinum neurotoxin	Abstract only	
Clemens 2012	CEA; sacral neuromodulation, botulinum neurotoxin	Abstract only	

Corcos 2012	CEA; sacral neuromodulation, botulinum neurotoxin	Abstract only	
Creasey 2001	CEA; sacral neuromodulation, botulinum neurotoxin	Wrong indication	Cord injury patients
D'Ausilio 2012	CEA; sacral neuromodulation, botulinum neurotoxin	Abstract only	
Dandolu 2015	Real-world effectiveness; sacral neuromodulatio	Abstract only	
Dmochowski 2017	CEA; percutaneous tibial nerve stimulation, sacral neuromodulation, botulinum neurotoxin, best supportive care	Abstract only	
Ecri 2005	HTA; sacral neuromodulation	Unable to obtain full text	
Ecri 2000	HTA; sacral neuromodulation	Unable to obtain full text	
Errando-Smet 2014	CEA; botulinum neurotoxin	Abstract only	Sacral neuromodulation was only a downstream treatment option
Espinosa 2016	Budget impact analysis; mirabegron, antimuscarinic, botulinum neurotoxin, sacral neuromodulation, and percutaneous tibial nerve stimulation	Abstract only	
Futaba 2011	Effectiveness (and costs) of transcutaneous sacral nerve stimulation and sacral nerve stimulation	Abstract only	
Ganz 2011	CEA; sacral neuromodulation, botulinum neurotoxin	Abstract only	
Harry 2015	CEA; sacral neuromodulation, botulinum neurotoxin	Abstract only	
Hartmann 2009	review; sacral neuromodulation, botulinum neurotoxin	Wrong study design	review
Harvie 2018a	CMA; sacral neuromodulation, botulinum neurotoxin	Abstract only	

Harvie 2018b	CMA; sacral neuromodulation, botulinum neurotoxin	Abstract only	
Hassouna 2012	CEA; sacral neuromodulation, botulinum neurotoxin	Abstract only	
Healthcare Insurance Board/College voor zorgverzekeringen/Medical Services Advisory Committee 1985	HTA; sacral neuromodulation, botulinum neurotoxin	Wrong date	Published before 2000
Hepp 2016	CEA; sacral neuromodulation, percutaneous tibial nerve stimulation, and botulinum neurotoxin	Abstract only	
Hessami 2016	CEA; sacral neuromodulation, percutaneous tibial nerve stimulation, botulinum neurotoxin, and best supportive care	Abstract only	
Hinnenthal 2013	PRO study and CMA; sacral neuromodulation	Abstract only	
Jenks 2013	CEA; sacral neuromodulation, percutaneous tibial nerve stimulation, botulinum neurotoxin	Abstract only	
Klotz 2007	Cost of illness study; no treatment broken out (only devices as a group)	Wrong study design	
Leng 2099	CEA; sacral neuromodulation, botulinum neurotoxin	Abstract only	
Leong 2099	CEA; sacral neuromodulation, botulinum neurotoxin	Abstract only	
Loveman 2014	Budget impact analysis; sacral neuromodulation, botulinum neurotoxin	Abstract only	
MacDiarmid 2010	CEA; p ercutaneous tibial nerve stimulation and sacral neuromodulation	Abstract only	
Murray 2014	CMA; mirabegron, botulinum neurotoxin, and sacral neuromodulation	Abstract only	
National Institute for Clinical Excellence 2004	Clinical guidance	Wrong study design	

Nazir 2015	CEA; oral anti-muscarinic agents, β3-adrenoceptor agonist, mirabegron	Wrong intervention	
Ng 2017	Budget impact analysis; sacral neuromodulation, botulinum neurotoxin	Abstract only	
Ockrim 2013	CEA; sacral neuromodulation, percutaneous tibial nerve stimulation, and botulinum neurotoxin	Abstract only	
Patel 2018	Cost analysis; sacral neuromodulatio	Abstract only	
Pichon Riviere 2011	HTA; sacral neuromodulation	Wrong language	Spanish language
Sanford 2014	Review; various treatments	Wrong study design	Review
Thomas 2010	CMA; transcutaneous electrical sacral nerve stimulation and sacral neuromodulation	Abstract only	
Watanabe 2009	CMA; sacral neuromodulation, botulinum neurotoxin, and augmentation cystoplasty	Abstract only	
Wielink 1997	CEA; sacral rhizotomies and electrical bladder stimulation	Wrong year	Before year 2000
Wood 2019	Database study determining frequency of various treatments	Abstract only	
Medical Technology Unit - Swiss Federal Office of Public Health	n.a.	Unable to obtain full text	
Blue Cross and Blue Shield Association. Medical Advisory Panel 2000	n.a.	Unable to obtain full text	
Blue Cross and Blue Shield Association. Medical Advisory Panel 1998	n.a.	Wrong year	Before year 2000

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

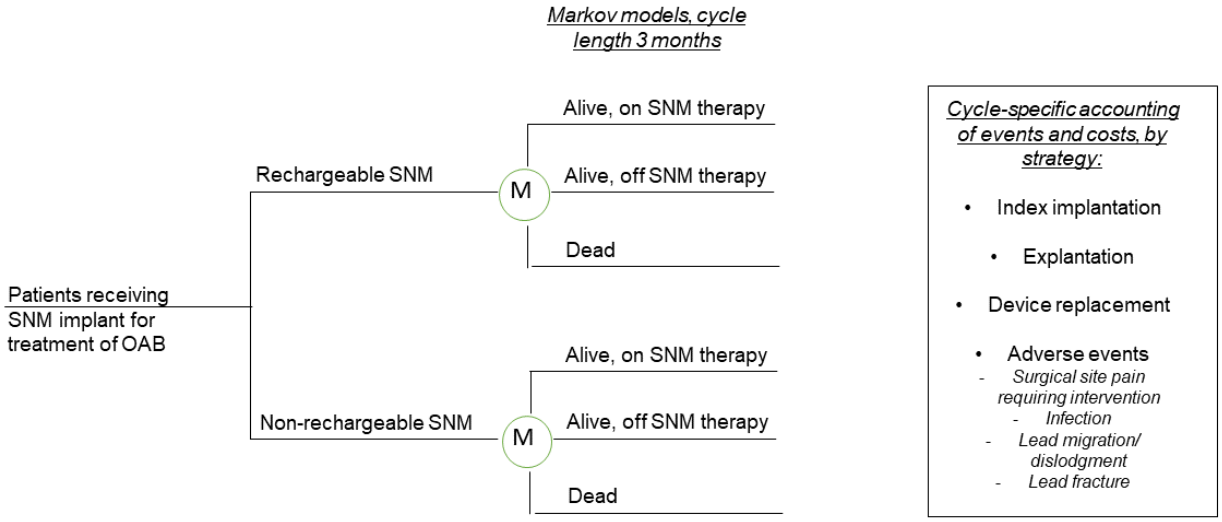


Structured abstracts for unpublished studies

Unpublished studies were only considered for the clinical evidence synthesis.

Appendix B: Model structure

Please provide a diagram of the structure of your economic model.



Appendix C: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☐ If no, please proceed to declaration (below)

Yes ☒ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information provided in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
#64/65, 70	☒ Commercial in confidence ☐ Academic in confidence	Commercial in confidence – sensitive research and development data.	No limit in time – indefinite confidentiality.
Details	Testing methodology and results are central in Axonics' research and development strategy, and therefore constitute sensitive information. The Axonics Neurostimulator's 15+ years longevity claim has been approved by both its CE Mark in Europe (BSI), its Health Canada License, its TGA Approval in Australia, its FDA PMA Approval in the US and appears on the product labelling in all these geographies. Therefore, testing details provided in this application are a courtesy of Axonics, with the aim to explain to NICE how the claim for 15+ years longevity was approved. Given this information is sensitive and only supports an already approved claim, Axonics would like it to remain confidential.		
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*		**Date:**	October 2, 2019
Print:	Karen L. Noblett, M.D.	**Role / organisation:**	Chief Medical Officer, Axonics Modulation Technologies
Contact email:	knoblett@axonics.com		

NICE National Institute for Health and Care Excellence

Medical technologies guidance

Collated expert questionnaires

Technology name & indication: Axonics sacral neuromodulation system for overactive bladder and faecal incontinence

Experts & declarations of interest (DOI)

Expert #1	Andrew Thorpe, Consultant Urologist, Freeman Hospital Newcastle.
	DOI: Yes, a clinical fellow in my department has been supported salary wise (0.5) by an educational grant from Medtronics
Expert #2	Jane brocksom, Senior clinical nurse specialist, Leeds teaching hospital NHS trust.
	DOI: NONE
Expert #3	Karen Nugent, Senior lecturer, University of Southampton.
	DOI: NONE
Expert #4	Dermot Burke, Associate Professor in Clinical Surgery, Leeds Teaching Hospitals NHS Trust.
	DOI: NONE
Expert #5	Nikesh Thiruchelvam, Con Urol, Cambridge University Hospitals NHS Trust.
	DOI: Yes, Medtronic funded dinner and course (unrestricted educational grant) 2013/14
Expert #6	Chris Harding, Consultant Urological Surgeon, Newcastle-upon-Tyne Hospitals NHS Foundation Trust, Chairman – British Association of Urological Surgeons subsection of Female, Neurological and Urodynamic Urology
	DOI: Yes, since 2015 my trust has been paid for me acting as a Proctor for Medtronic
Expert #7	Julie jenks, Advanced nurse practitioner, University College London Hospitals NHS Foundation Trust, London UK.
	DOI: Yes, non funded/non paid involvement in research projects for both Axonics and Medtronic on Sacral neuromodulation.
Expert #8	Mohammed Belal, Consultant Urological Surgeon, University Hospitals Birmingham.
	DOI: Yes, speaker for Medtronic 2018

Expert #9	Ased Ali, Consultant Urological Surgeon, Mid Yorkshire Hospital NHS Trust, British Association of Urological Surgeon
	DOI: NONE
Expert #10	Nicholas Fletcher, Urology Surgical Care Practitioner, Salford Care Organisation.
	DOI: Yes, paid teaching session for Medtronic – PNE under LA in clinic setting, 21 November 2019.
Expert #11	Mahreen Pakzad, Consultant Urological Surgeon, University College Hospital London NHS Trust
	DOI: Yes, CI for female retention case series study, PI for Artisan clinical trial.

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1. **Please describe your level of experience with the technology, for example: Are you familiar with the technology? Have you used it? Are you currently using it? Have you been involved in any research or development on this technology? Do you know how widely used this technology is in the NHS?**

Expert #1	I am an experienced clinician in treating patients with overactive bladder causing urinary incontinence and have implanted a large number of Medtronic permanent stimulators I have not used the Axionics stimulator, and I have not been involved in research into this new stimulator The technique of SNS for urinary and faecal incontinence is used in a number of specialist referral centres for these problems – it is only carried out in specialist secondary care centres
Expert #2	I am familiar with the technology, I have used similar products for 8years and I am currently using this newer technology. I have not been involved in any research during its development. Sacral Nerve Modulation/stimulation is widely used within the NHS by urologists with a specialist interest in pelvic floor dysfunction
Expert #3	Yes – our hospital did the pilot study of the first 10 used for faecal incontinence We have subsequently implanted further devices I have not been involved in research or development Few centres

Expert #4	I have not used this particular device, but am very familiar with the treatment of sacral neuromodulation for faecal incontinence. I have not been involved with any research or development for this particular device. It is not currently used routinely, as far as I am aware, within the NHS.
Expert #5	Yes, familiar Not used it Not using it currently Initially approached as a UK site but then company used UCLH Yes, not widely adopted at present
Expert #6	Familiar with the technology but have not used the Axonics system. Large experience of Sacral Neuromodulation. Not involved in the development of the technology. I do know that some units are using Axonics in the NHS as part of regulated clinical trials but I am not sure if anyone is using it in routine practice.
Expert #7	yes - yes -yes -research using it. -neuromodulation is widely used, Axonics not widely used as Medtronic are the market leader.
Expert #8	I am familiar with the technology as I use the current equivalent technology that is already well established. I have not used the axionics technology yet I was involved in the discussion of the initial trial but this did not progress Limited use in the NHS

Expert #9	I am familiar with sacral neuromodulation and regularly use the Medtronic kit. I have some familiarity with the Axionics kit but it is not currently the main kit used in our hospital. Sacral nerve modulation is used widely in the NHS but Medtronic was the only provider until 2017 and therefore most trusts will still be using the Medtronic kit as it has been the standard of care. Axionics is a new but welcome entrant into the field which was previously monopolised by Medtronic
Expert #10	Yes we have implanted the permanent Axonics SNM device at SHO. To date with have placed 10 devices. To date we have not been involved in any research projects on this device. As for how widely used the devices is, I do not have any factual statistics on this. I am aware of a number of centres however that are utilising this device.
Expert #11	Very familiar with the technology have used it for 18 months and am involved in 2 clinical trials using the technology. The basic tech is widespread throughout the NHS but this device is used more in colorectal surgery for patients with faecal incontinence for example.

2. Has the technology been superseded or replaced?

Expert #1	No
Expert #2	In my opinion, the new technology will work alongside the existing technology, it will be a competitor product rather than supersede or replace
Expert #3	No but Medtronics are looking to launch an MRI compatible rechargeable SNS device soon
Expert #4	no
Expert #5	No
Expert #6	No
Expert #7	no

Expert #8	No
Expert #9	No
Expert #10	Currently it is an option for the patient to choose between the Axonic and Medtronic's devices after a brief explanation of the facts and general differences between the two.
Expert #11	No

Current management

3. How innovative is this technology, compared to the current standard of care? Is it a minor variation or a novel concept/design?

Expert #1	The innovation is in its rechargability which should give it a longer clinical life than the current non rechargeable stimulator
Expert #2	The new technology (Axonics) offers a variation on what is currently available (Medtronic)
Expert #3	Minor variation – rechargeable smaller device which is MRI compatible otherwise the same
Expert #4	The technology should be considered a minor variation. The advance is in the battery, with the innovation being development of a rechargeable battery. This means that the patient needs fewer operations to change the implanted battery.
Expert #5	The idea of stimulating S3 nerve for OAB symptoms is the same as existing technology. The stimulation by a tined lead is the same. The differences to existing technology is how the electrical stimulation is provided to the tined lead by the implantable pulse generator (IPG) and how the patient can alter the stimulation parameters
Expert #6	Minor but important variation (in my opinion)
Expert #7	The new axonics device is Novel, because of rechargeable nature, size and MRI compatible. It is behind/old-fashioned in some of the technology. The pt is limited because they cannot change settings remotely. It only allows one stored programme for the patients so means multiple hospital trips if the patient isn't getting an optimum outcome.

	The hand held clinical programmer is complex, heavy and 'clumsy' to use initially.
Expert #8	It is a minor variation
Expert #9	The Axionics implant has the advantage of much smaller size (therefore increased patient comfort), a rechargeable battery (therefore no need for replacement) and MRI compatibility (a major downside to the Medtronic implant).
Expert #10	The option for rechargeable function reduces the potential for more surgery, if not prolongs the interval in-between them due to not requiring surgery to replace spent battery. The ability for patient to be able to still under go MRI scans is also a potential benefit for the patient.
Expert #11	Novel concept.

4. Are you aware of any other competing or alternative technologies available to the NHS which have a similar function/mode of action to the notified technology? If so, how do these products differ from the technology described in the briefing?

Expert #1	The only competition would be the current non-rechargeable Medtronic SNS so as above the advantage to the patient would potentially be a longer lasting stimulator which would not need to be changed so frequently
Expert #2	The existing Medtronic product is the only one to my knowledge used on bladder dysfunction, the new Axonics product gives an alternative. I understand it is a market widely being researched and viewed by other companies so there maybe more competitors in the future. The 2 products offer very similar function and modes of action, the difference as I see it is the option to recharge the implanted impulse generator/battery
Expert #3	Interstim 2 is the other device used at present
Expert #4	No I am not aware
Expert #5	Sacral nerve stimulation by Medtronic

	As above
Expert #6	Yes – Medtronic SNS system (Interstim) The Axonics system differs in that it is rechargeable and (I think) MRI compatible.
Expert #7	Medtronics established system Medtronics new Interstim Micro awaiting product launce (Dec 2019) which *claims* to be the same (or better) than the rival Axonics
Expert #8	No
Expert #9	The Medtronic Interstim is used for the same group of patients but the Axionics implant has the advantages mentioned in number 3.
Expert #10	The Medtronic interstim II is the only current alternative that is similar. This is the established SNM device but is not rechargeable or MRI compatible. Other technologies around nerve stimulation include the PTNS which can be used for the treatment of OAB but not Fowler's syndrome (Female non-obstructive retention) patients.
Expert #11	No

Potential patient benefits

5. What do you consider to be the potential benefits to patients from using this technology?

Expert #1	As above
Expert #2	The option to undergo an full body MRI and rechargeable battery appears to be the 2 main benefits
Expert #3	The non rechargeable unit needs to be replaced 5-8 yearly. The projection on this rechargeable unit is 15 years. MRI compatibility means device explanation does not need to occur before MRI can be undertaken

Expert #4	The main benefit would be a longer lifespan of the implanted battery, and therefore fewer operations to change it.
Expert #5	Rechargeable IPG (so in theory longer lasting) Smaller IPG (less pain/discomfort) MRI compatible tined lead
Expert #6	Rechargability means much less frequent battery changes which for other non-rechargable systems would be every 3-5 years and necessitates an operation.
Expert #7	Rechargeable is better to avoid reoperation if the patient is happy to charge once per week. Claims that the Axonics battery last 15years are unsubstantiated to the best of my knowledge. The Medtronic device lasts 3-5years.
Expert #8	Longer battery life
Expert #9	Greater comfort, no need for battery replacement at end of life, ability to have MRI scans which have become the standard of care for diagnostics in multiple pathologies.
Expert #10	The ability to potentially reduce number of surgeries and if required the ability to have MRI scan without having to have the device removed.
Expert #11	Smaller battery Longer duration between battery exchanges compared with existing technology.

6. Are there any groups of people who would particularly benefit from this technology?

Expert #1	Patients with urinary incontinence – the evidence for faecal incontinence is at best sparse
Expert #2	No, I am not aware of any
Expert #3	Those who wish to have less operations and are happy to recharge the unit every week
Expert #4	No

Expert #5	Patients who may need MRIs in the future
Expert #6	If it is MRI compatible then those with need for regular MRI scans who would not be eliginle for SNS using traditional systems.
Expert #7	Anaesthetic risk patients, those with low BMI
Expert #8	Low BMI patients
Expert #9	Those likely to need an MRI in the future (patients with back problems, neurological problems, pelvic pathology including prostate cancer). Those finding the current large implant painful.
Expert #10	Patients who require MRI investigation for various conditions.
Expert #11	Patients with overactive bladder, urinary retention, faecal incontinence, constipation and potentially those with bladder pain (chronic).

7. Does this technology have the potential to change the current pathway or clinical outcomes? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?

Expert #1	It would not change the current referral pathway, but it may potentially lead to fewer overall hospital visits in terms of operations if the stimulator needs to be changed less often I think the OPD visits would remain fairly similar as the patients would still need a yearly routine FU appointment once they are established on this treatment
Expert #2	Yes, potentially but we would need to see more patients and have longer patient evaluations to be sure
Expert #3	Less operations over a 15 years period
Expert #4	As fewer operations would be needed, then it should lead to fewer hospital visits and less invasive treatment overall. However, clinical outcomes are not likely to be any different.
Expert #5	Yes, current Medtronic technology involves a change of the IPG at 4-6 years (and so a GA operation and costs of new IPG, approximately £7000), the rechargeable IPG with Axonics is supposed to last upto 11 years.

Expert #6	Fewer in patient episodes for battery replacement.
Expert #7	*Fewer* General anaesthetics if the battery lasts 15 years. *More* hospital visits as the device stores only one programme so reprogramming and switching throught different electrode setting may require a lot more OPD visits then with the current Medtronic system. Outcomes will be the *same* as it's the lead placement that is crucial and to the best of what I have seen the lead and operation kit is the 'same' as Medtronic's.
Expert #8	No
Expert #9	Yes: • Implant pain less likely due to the compact size • Battery replacement not routinely necessary as rechargeable Implant not likely to need removal for MRI.
Expert #10	I believe less invasive treatments as mentioned above.
Expert #11	Yes

Potential system impact

8. What do you consider to be the potential benefits to the health or care system from using this technology?

Expert #1	I cannot see any harm from this treatment it is already well established
Expert #2	The option to undergo an MRI scan without fear the SNM will be damaged and need replacing is a huge benefit – potentially reducing costly follow-up or reimplantation
Expert #3	Cost less due to cost of operation and replacement battery

Expert #4	Fewer hospital visits and operations, therefore potentially less expensive. The details would need to be examined careful by someone with a good grasp of health economics
Expert #5	As 7.
Expert #6	See above – the longer lasting battery may have an economic benefit but I do not know the relative costs of Axonics vs other systems.
Expert #7	*Fewer* General anaesthetics if the battery lasts 15 years. Outcomes will be the *same* as it's the lead placement that is crucial and to the best of what I have seen the lead and operation kit is the 'same' as Medtronic's.
Expert #8	Longer battery life
Expert #9	Less hospital visits for further surgery
Expert #10	There is a potential financial saving both from the cost of replacing batteries and the reduction in theatre use as a result.
Expert #11	Lower costs to NHS due to longer battery life

9. Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the technology likely to cost more or less than current standard care, or about the same?

Expert #1	It could potentially cost less in the longer term if less stimulators need to be re-implanted
Expert #2	Not sure, hopefully in the long term potentially reduce cost but difficult to be sure
Expert #3	less
Expert #4	See my answer to Q8. I am not aware how the cost of the new device compares to what is currently available. This cost will make a substantial contribution to any potential savings.

Expert #5	Less if the IPG lasts longer
Expert #6	Theoretically less but depends on individual unit cost of SNS system.
Expert #7	*Same* for the operation *More* for the follow ups in the specialist clinics *Less* for reoperation based on the need for battery exchange (assuming Axonics lasts 15years).
Expert #8	The same cost
Expert #9	Cost less due to less need for surgical removal or revision of implant. Interstim battery lasts around 5-years then require surgery for replacement.
Expert #10	It would appear the cost would be less than the current situation but this is yet to be proven.
Expert #11	LTM- Less

10. What do you consider to be the resource impact from adopting this technology? Could it, for example, change the number or type of staff needed, the need for other equipment, or effect a shift in the care setting such as from inpatient to outpatient, or secondary to primary care?

Expert #1	There will be no increase in resource I think it will be resource neutral
Expert #2	The same amount of staff – urologist, nurse specialists to run the service, not sure if it could move beyond secondary care for implantation or for specialist dedicated nurse follow-up. It is a specialist service needing planned, timed and possibly same day follow-up for the life it is implanted
Expert #3	Apart from replacing battery – little other impact
Expert #4	I do not consider that the technology will make a substantial impact to the resources required for this treatment

Expert #5	Will depend on tariff of new device
Expert #6	Minimal
Expert #7	Same staff needed. Same equipment Shift from remote (outreach) to needing to be outpatient based (Medtronic system allows four programmes to be stored, so I can liaise with pts remotely (from their home) and change their setting with them over the phone. You cannot do this with the axonics system so they need to attend the hospital for every change of setting. This is a major resource impact. Over half of the patients need reprogramming during their first five years.
Expert #8	No change
Expert #9	One would expect slightly less theatre resource to be needed as revision and removal rate would likely be less.
Expert #10	Theatre time potentially being saved would appear to be the biggest benefit at this time.
Expert #11	Less contact with surgeon, more contact or same degree of contact with Nursing Staff.

11. Are any changes to facilities or infrastructure, or any specific training needed in order to use the technology?

Expert #1	no
Expert #2	No just Axonics equipment
Expert #3	no
Expert #4	Patients will need to be trained to recharge the battery. I do not expect that this will be costly or time-consuming
Expert #5	No
Expert #6	No

Expert #7	Just training on the hand held device and controller.
Expert #8	Retraining of the staff to use the technology and program
Expert #9	Basic training in terms of the differences in this kit compared to Medtronic. Axionics have already been providing this.
Expert #10	Only the use of the patient programming technology.
Expert #11	Training in surgical technique, and programming.

12. Are you aware of any safety concerns or regulatory issues surrounding this technology?

Expert #1	No
Expert #2	No it all appears very safe and gives patients excellent results if implanted by trained specialist and nursing follow-up with interested and keen specialist nurses.
Expert #3	no
Expert #4	No, I am not.
Expert #5	No
Expert #6	No
Expert #7	No
Expert #8	No
Expert #9	No.
Expert #10	Not to date.
Expert #11	No

General advice

13. Please add any further comments on your particular experiences or knowledge of the technology, or experiences within your organisation.

Expert #1	Nil else to add in
Expert #2	The technology is designed to be used simply on patients with complex bladder dysfunction
Expert #3	none
Expert #4	
Expert #5	Nil
Expert #6	Nil to add
Expert #7	Yes, see comment 10 and 7
Expert #8	Main concern is the lack of medium and long term data. Battery life claims are difficult to be verify clearly as the device has only been on the market for a short time.
Expert #9	We believe this to be a very useful addition to the option available in sacral neuromodulation. This is the first significant innovation within this area in over decade. Medtronic's monopoly position as sole provider as resulted in no pressure to innovate and improve

	their existing Interstim device despite the fact that MRI compatibility has been feasible for many years (as evidenced in the deep brain stimulation implant which is technologically very similar and also produced by Medtronic).
Expert #10	Implanting this device is very similar to the Interstim II.
Expert #11	Small battery is liked by patients

Other considerations

14. Approximately how many people each year would be eligible for intervention with this technology, either as an estimated number, or a proportion of the target population?

Expert #1	I do not think there would be any change in the gross number of patients undergoing SNS for urinary incontinence – there is already a stringent set of criteria for patients to be put forward for it and this new tech will not change it
Expert #2	Sorry, Unable to answer - the number of patients we trail has risen and those with permanent implanted SNM equipment is continuing to be an option chosen by patients primarily as a minimally invasive option
Expert #3	Patients could be allowed to choose whether they would prefer a no rechargeable device that will need replacing or commit to a weekly recharging time and have less operations
Expert #4	It would potentially apply to 100% of those with an implanted neuromodulator. This would be approximately 400 – 600 people in England per year.
Expert #5	Currently 400 SNS cases in UK per year for OAB/urinary incontinence
Expert #6	I don’t know
Expert #7	100
Expert #8	

Expert #9	Approximately one third of patients undergoing treatment for overactive bladder are refractory to pharmacological management and would potentially be eligible for this type of treatment under current NICE guidelines.
Expert #10	In this Trust's area, I would estimate 25-30 per anum.
Expert #11	80%

15. Would this technology replace or be an addition to the current standard of care?

Expert #1	Probably and addition the Medtronic stimulator is well established and has a lot of data to back it up so I think it will increase choice of technology only.
Expert #2	It would be an addition
Expert #3	replacement
Expert #4	If effective, it is likely to replace the current non-rechargeable battery
Expert #5	Addition
Expert #6	Potentially replace
Expert #7	addition
Expert #8	Additional to standard care
Expert #9	This technology provides both an alternative to the previous monopoly provider as well as some specific advantages/
Expert #10	Currently an addition but could become the standard in time.
Expert #11	Addition to current standard of care.

16. Are there any issues with the usability or practical aspects of the technology?

Expert #1	no
Expert #2	Non
Expert #3	no
Expert #4	No that I can see.
Expert #5	I am not clear how good the evidence is of how long the device (IPG) is expected to last
Expert #6	I don't know
Expert #7	Yes, see comment 10 and 7
Expert #8	No
Expert #9	Nothing specific.
Expert #10	Not to date
Expert #11	No

17. Are you aware of any issues which would prevent (or have prevented) this technology being adopted in your organisation or across the wider NHS?

Expert #1	no
Expert #2	Non
Expert #3	no
Expert #4	No
Expert #5	No

Expert #6	No
Expert #7	No
Expert #8	No
Expert #9	Existing familiarity with the Medtronic kit creates some resistance to changing over to this kit.
Expert #10	Only issue for funding is for the Fowler syndrome cohort of patients that require individual funding requests to be generated, this is time consuming and frustrating process.
Expert #11	No

18. Are you aware of any further evidence for the technology that is not included in this briefing?

Expert #1	no
Expert #2	No
Expert #3	no
Expert #4	No
Expert #5	Evidence not included in briefing
Expert #6	No
Expert #7	no
Expert #8	No
Expert #9	No
Expert #10	Not at this time.

Expert #11	No

19. Are you aware of any further ongoing research or locally collected data (e.g. audit) on this technology? Please indicate if you would be able/willing to share this data with NICE. Any information you provide will be considered in confidence within the NICE process and will not be shared or published.

Expert #1	no
Expert #2	Not aware of any
Expert #3	WE are collecting data but on small numbers at present
Expert #4	We have no locally collected data. The centre with the most experience in the UK is Southampton. There may be some audit data from there. A review of the literature has not revealed any new, sound evidence since the NICE report of 2018.
Expert #5	Current trial in UCLH of RCT between Medtronic and Axonics devices
Expert #6	No
Expert #7	Research project on urinary retention in our centre using Axonics Amplitude trial using Medtronic system at our centre.
Expert #8	UCH are collecting data.
Expert #9	No
Expert #10	We intend to Audit the performance of this device against the establish device over the next twelve months.
Expert #11	Personal data from case series. Yes willing to share.

20. Is there any research that you feel would be needed to address uncertainties in the evidence base?

Expert #1	We will need further longitudinal patient studies to look at the long term outcomes and the true replacement/explantation rates with this new tech. a randomised trial of Axionic v's Medtronic tech is not feasible
Expert #2	I wish to see more extensive independent work carried out, on how long, in years, the rechargeable battery works for. I am sceptical – I use my phone battery as a comparison and after 2 years it is beginning to not last as long.
Expert #3	no
Expert #4	A trial of the current device against the new device that looked at cost-effectiveness over a prolonged period e.g. 20 years (to encompass the stated 15 year lifespan of the new device) would be useful.
Expert #5	Await above trial Use of device in urinary retention and faecal incontinence
Expert #6	Economic analysis of Axonics vs Metronic Interstim system
Expert #7	Yes, the evidence for the battery life of the Axonics system being 15years.
Expert #8	Yes, larger trials with medium and long term data
Expert #9	No
Expert #10	The comparison between devices' performance and patients overall satisfaction with them.
Expert #11	Need LTM SAFETY AND EFFICACY DATA.

This report was generated on 13/11/19. Overall 8 respondents completed this questionnaire. The report has been filtered to show the responses for 'All Respondents'.

The following charts are restricted to the top 12 codes. Lists are restricted to the most recent 100 rows.

Have you used the Axonics sacral neuromodulation (SNM) device, which needs to be charged every 2 weeks, for urinary retention and symptoms of overactive bladder?

What do you consider to be the benefits **of Axonics SNM for urinary retention and symptoms of overactive bladder?**

These might include the effect of Axonics SNM on: (Physical symptoms, level of disability, pain, mental health etc.)

This is a sacral neuromodulation device, similar to the Medtronic device already in regular clinical use in the UK. It is used for treatment of urinary incontinence and also for female urinary retention.
Less physical symptoms of OAB
reduced urge incontinence and leakage
have to wear a nappy when go out, leak when walking

What do you consider to be the benefits of Axonics SNM for urinary retention and symptoms of overactive bladder?

These might include the effect of Axonics SNM on: (Quality of life (e.g. lifestyle, work, activities of daily living etc.))

Improved. This is a slightly meaningless question
Quality of life improved. Like being in control - better mental health
Improved
Completely life changing,
quality of life
less travel

What do you consider to be the benefits of Axonics SNM for urinary retention and symptoms of overactive bladder?

These might include the effect of Axonics SNM on: (How quickly symptoms resolve)

Few days
Symptoms resolved within 2 months - less appointments
Symptoms improved by 80% my bladder effected on a daily basis previously, i was passing urine 16-20 times oer day, 3 times per night and multiple leeks. I now go approx 6-8 times per day, 1-2 per night, limited leakage

What do you consider to be the benefits of Axonics SNM for urinary retention and symptoms of overactive bladder?

These might include the effect of Axonics SNM on: (Greater convenience or comfort of their treatment (e.g. outpatient rather than inpatient, quicker, less travel/expense involved for them and their carers/family))

Greater convenience compared to what? Most patients find the treatment effective in controlling their symptoms.
It has been a complete success, no other RX had helped my symtoms previously

What do you consider to be the disadvantages **of Axonics SNM for urinary retention and symptoms of overactive bladder?**

These might include the effect on: (Physical symptoms, level of disability, pain, mental health etc.)

May get device related pain. Sam as for Medtronic sacral neuromodulation
Sightly limited on work as can't heavy lift or over stretch - shouldn't be on beltline as can be painful
Having the operation, I am very active and have had to change stop some types of physical activity
pain
none

What do you consider to be the disadvantages of Axonics SNM for urinary retention and symptoms of overactive bladder?

These might include the effect on: (Quality of life (e.g. lifestyle, work, activities of daily living etc.))

N/A

What do you consider to be the disadvantages of Axonics SNM for urinary retention and symptoms of overactive bladder?

These might include the effect on: (How quickly symptoms resolve)

N/A
Symptoms improved within the 1st week

What do you consider to be the disadvantages of Axonics SNM for urinary retention and symptoms of overactive bladder?

These might include the effect on: (Greater convenience or comfort of treatment (e.g. self-administered rather than inpatient, quicker, less travel/expense involved for them and their carers/family))

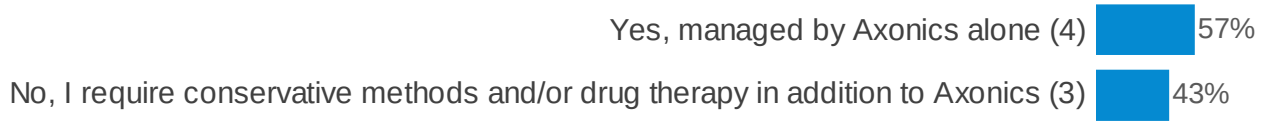
This doesn't make sense, as greater convenience is not usually a disadvantage
My first wire also broke so had to have another op to eplace - all ok now- all worth it. The Axoinics device is very easy and convenient and being able to change the settings via a remote very useful
traveling

After the device was implanted, have you needed further procedures to replace or adjust it?

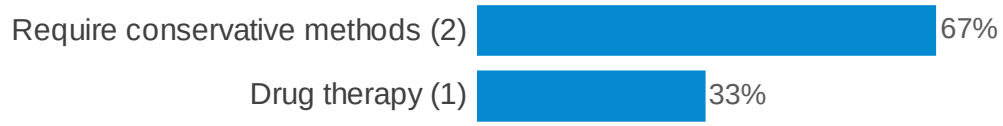
How often do you visit your clinician to reprogramme the device?

Usually not. 20% risk of needing revision surgery - same as for Medtronic device
at the moment 6 weeks
Twice in the first 3 months, not needed to do since
Not yet - appointment 22 Oct 2019 - too early to say
1 set wire broke, I am also part of the Axonics trial so had regular appointments
Every 4 weeks at present
6 monthly
3-6 months

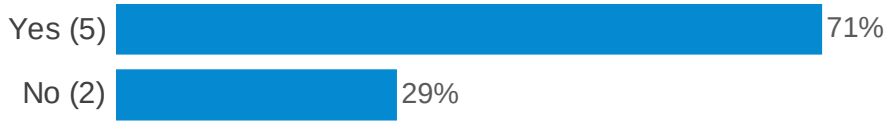
Are your symptoms managed by Axonics alone or do you require conservative methods and/or drug therapy in addition to Axonics? (please tick all that apply)



Please confirm which you use in addition to Axonics? (please select all that apply)



Would you recommend it to other people with the same condition as you?



Please explain your answer:

I am a doctor, not a patient.

Re: symptom management: lifestyle changes which include type of exercise, reduced caffeine

Are there any other technologies for urinary retention and symptoms of overactive bladder which you've heard about that you would consider more beneficial for NICE to develop guidance on?

Please explain your answer:

I have tried bladder botox 3 times and TENS once. need more info on these for others as consultants not fully sure

National Institute for Health and Care Excellence
Patient Organisation Submissions for Medical Technologies - Submission Template

NICE Medical Technologies Advisory Committee

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

Please read the guide to completing a submission fully before completing this template.

Information about your organisation	
Organisation name	Bladder Health UK
Contact person's name	Susannah Fraser
Role or job title	Communication & Media Manager
Email	[redacted]
Telephone	0121-702-0820
Organisation type	Patient/carer organisation (e.g. a registered charity) ×☐ Informal self-help group ☐ Unincorporated organisation ☐ Other, please state:
Organisation purpose (tick all that apply)	Advocacy ☐x Education ☐x Campaigning ☐x Service provider ☐ Research ☐x Other, please specify:
What is the membership of your organisation (number and type of members, region that your organisation represents, demographics, etc)? We have approximately 2,000 members, 1,500 of whom are patients/sufferers and approximately 5,000 followers on social media. Our sufferers are predominantly women but approximately 10% are male. We have members from all over the UK.	

Please note, all submissions will be published on the NICE website alongside all evidence the committee reviewed. Identifiable information will be redacted.

National Institute for Health and Care Excellence
Patient Organisation Submissions for Medical Technologies - Submission Template

If you haven't already, please register as a stakeholder by completing the stakeholder registration form and returning it to medtech@nice.org.uk

Further information about registering as a stakeholder is available on the NICE website.

Did you know NICE meetings are held in public? You can register on the NICE website to attend a meeting up to 20 working days before it takes place. Registration will usually close 10 days before the meeting takes place. Up to 20 places will be available, depending on the size of the venue. Where meetings are oversubscribed NICE may need to limit the number of places we can offer.

Sources of information

What is the source of the information about patients' and carers' experiences and needs that are presented in this submission?

Patient experiences are gathered by the team during our conversations with them on our Advice Line. We regularly discuss treatment options with out members. The Advice Line is open give days a week between 9.30am and 2.00pm

National Institute for Health and Care Excellence
Patient Organisation Submissions for Medical Technologies - Submission Template

Impact of the symptoms, condition or disease

1. How do symptoms and/or the condition or disease affect people's lives or experiences?

Overactive bladder is not curable and can be challenging to manage. Without treatment OAB can leave sufferers feeling embarrassed, stressed, tired, depressed and alone. Those who have the associated Nocturia can suffer from chronic fatigue and have difficulty performing day to day activities. The elderly are at risk of falls while getting up a night.

Many sufferers restrict their fluid intake before going out for fear of 'accidents' and are constantly looking for toilets while out of the house. Some withdraw from social interaction completely and become housebound.

2. How do symptoms and/or the condition or disease affect carers and family?

The condition is extremely disruptive to normal living. It affects personal relationships, travel, holidays and work life for everyone involved.

3. Are there groups of people that have particular issues in managing their condition?

The elderly are particularly at risk of falls during the night with this condition leading to broken bones and hospital care.

Experiences with currently available technologies

4. How well do currently available technologies work?

When conservative measures such as diet are unsuccessful, sufferers are generally directed to take anticholinergic medication. This can be successful but the side effects (dry mouth, constipation etc) can sometimes become intolerable. Anticholinergics have recently been implicated in the on-set of dementia making them less attractive to the older generation. Betimga, a bet 3-adrenocepter has recently been introduced to the market but this also has side effects which make it impossible for some to take. Botox which is now offered can be effective but it can cause serious issues with retention, is invasive and needs to be repeated in a hospital setting. Similarly, the present InterStim device is also an option although a surgical procedure to replace the batteries is required every five years.

5. Are there groups of people that have particular issues using the currently available technologies?

The elderly due to the dementia risk of some of the available medications.

About the medical technology being assessed

6. For those <u>with</u> experience of this technology, what difference did it make to their lives?

7. For those <u>without</u> experience of the technology being assessed, what are the expectations of using it?

We have no experience of Axonics Sacral Neuromodulation System but we would hope it would improve the quality of life for those with overactive bladder in a similar way to the InterStim device.

8. Which groups of people might benefit most from this technology?

Those with overactive bladder who do not respond to the first line therapies such as diet modification, anticholinergics or Betmiga.

Additional information

9. Please include any additional information you believe would be helpful in assessing the value of the medical technology (for example ethical or social issues, and/or socio-economic considerations)

Key messages

10. In up to five statements, please list the most important points of your submission.

- **Overactive bladder has a significant negative impact on the lives of sufferers and can be challenging to manage particularly in the elderly.**

National Institute for Health and Care Excellence
Patient Organisation Submissions for Medical Technologies - Submission Template

- **The Sacral neuromodulation system can be a valuable addition to the treatment options for this condition, where more conventional treatments have failed.**
-
-

Thank you for your time. Please return your completed submission to medtech@nice.org.uk

Using your personal information: The personal data submitted on this form will be used by the National Institute for Health and Care Excellence for work on Medical Technologies (including Diagnostics Assessment) and will be held on the Institute's databases for future reference in line with our privacy notice.

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 10/10/19-29/10/19	**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**) Yes (**AA**)
14.	Sent 9/10/19-23/10/19 Responses received 10/10/19-29/10/19	**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)"	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) 80% Female (**AA**) We tend to see more female patients. OAB generally effect more female population. In regards to female retention, well that is obvious. (**NF**)

			c. "Overactive bladder (OAB)"?	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) 70% (**AA**) Unable to say (**NF**) c) 20% (**AA**) 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**) 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**)

				I believe effectiveness is broadly similar across the various groups although group a. with urge incontinence may do slightly less well due to severity of symptoms (**AA**).
15.	Sent 9/10/19-23/10/19 Response received 11/10/19-29/10/19	**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**) Gender, Age, BMI, Neurological disease, baseline symptom severity, proportion of patients with urinary incontinence, faecal incontinence, concomitant medications. (**CH**) Loss of effectiveness over time (**AA**)
16.	Sent 9/10/19-23/10/19 Responses received 11/10/19-29/10/19	**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**) Yes (**AA**)
17.	Sent 9/10/19-23/10/19 Responses received 10/10/19-29/10/19	**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**) Daycase (**AA**)

18.	Sent 9/10/19-23/10/19 Responses received 10/10/19-29/10/19	**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**) Slight effect (**AA**) 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**) May have some effect, much bigger impact is from patient selection. (**AA**)
19.	Sent 9/10/19-23/10/19 Responses received 11/10/19-29/10/19	**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**) Yes (**AA**) 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**) Yes (**AA**)
20.	Sent 9/10/19-23/10/19 Responses received 11/10/19-29/10/19	**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**) No (**AA**)
21.	Sent 9/10/19-23/10/19 Responses received 10/10/19-29/10/19	**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 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?	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 targeting. (**NF**) I do not have the expertise to answer these questions accurately – perhaps a radiologists opinion would be useful. (**CH**) Unsure as I have never seen any such images. (**AA**) b) This is possible (**NF**) The device itself is unlikely to obscure the relevant areas to be examined with MRI. (**CH**) Yes conceivably but probably only rarely. (**AA**) c) No (**KN**) No (**NT**) No (**AA**)

				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 10/10/19-29/10/19	**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**) Not aware of any significant differences currently but it is probably too early to tell. (**AA**) b) No adverse issue to date requiring intervention, however only been implanting since June and a small number. (**NF**) I would expect to see less issue relating to discomfort due to the size of the device. (**AA**)
23.	Sent 9/10/19-23/10/19 Responses received 10/10/19-29/10/19	**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) • 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?	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 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**) It is unlikely that I would implant in most of these cases except patients with neurological disease origins. I would certainly implant in patients with diabetes as this is a common co-morbidity. MS is more tricky but may consider on rare occasions depending on the type of MS. I have experience of managing some patients with bilateral stimulation but prefer not initiate such treatment. (**AA**) b) Influencing factors include – literature, peer experiences, manufacturers advice. (**NF**)
24.	Sent 9/10/19-23/10/19 Responses received 10/10/19-29/10/19	**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?	a) Not had any patients do this. (**KN**) Depends on where they keep it. (**NT**) No experience with Axonics system. (**CH**) This can happen. Education of the patient on their patient controller is essential. (**NF**) Not particularly likely (**AA**) a) Again this can happen but the patient needs to be educated enough to spot and trouble shoot issues like this. (**NF**) 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**) Discomfort or loss of efficacy (**AA**)

25.	Sent 9/10/19-23/10/19 Responses received 11/10/19-29/10/19	**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 27/10/19-29/10/19	**Expert advisers** Q&A via email	Marcelissen et al. (2018) describe the usual options for managing overactive bladder syndrome as: 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**) Yes, but would have urodynamics prior to third line surgical treatment. NIHR funded study (FUTURE) RCT of urodynamics versus no urodynamics prior to Botox, currently recruiting to target in UK. (**NT**) Yes it is an accurate reflection (**AA**).
28.	Sent 22/10/19-23/10/19 Responses	**Expert advisers** Q&A via email	SNM is recommended for patients whose condition (urge urinary incontinence) is	These patients have usually failed medications therefore almost always do not continue to take them. (**CH**)

	received 27/10/19-29/10/19		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? b) How might this impact on study outcomes?	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**) Ideally no, if successful outcome from SNS, no need for medications. (**NT**) Not usually (**AA**) b) Studies reporting SNM success should detail the numbers taking and types of medications. (**CH**) 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**) If taking medications, one wouldn't know if SNS test improvement was from medications or not. (**NT**) Most should not be taking medication (**AA**).
29.	Sent 22/10/19-23/10/19 Responses received 27/10/19-29/10/19	**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**) Yes (**NT**) Yes (**AA**)
30.	Sent 22/10/19-23/10/19 Responses received 27/10/19-29/10/19	**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**) Yes, increased risk of lead migration or IPG moving or causing pain over time from trauma. Minimal but present increased risk of infection. (**NT**) I am not aware of any (**AA**).

				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**) Tolerability issue as above. (**NT**) It seems unlikely. We have had patients with older Medtronic IPGs that have lasted almost a decade without issue. (**AA**)
31.	Sent 22/10/19-23/10/19 Responses received 27/10/19-29/10/19	**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**) If device working well and battery stopped working (this can be checked with Medtronic device) –change IPG only, not lead. This occurs in all successful cases. (**NT**). Yes, prior to replacement (**AA**) b) Leads are occasionally replaced due to damage from fall etc… (**NF**) Get replaced 1 in 3 (**KN**) If still has power in IPG, can change lead only. This probably occurs in 10%. (**NT**) Not usually. I would say <10% get replaced at the time of IPG replacement. Most leads that get replaced, do so because of damage or displacement following impact/trauma. (**AA**)

32.	Sent 22/10/19-23/10/19 Responses received 27/10/19-29/10/19	**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**) After test period, the tined lead is usually well imbedded and unlikely to move (so unlikely after 2-3 weeks). (**NT**) Just as likely any time (but it's not common). (**AA**)
33.	Sent 22/10/19-23/10/19 Responses received 27/10/19-29/10/19	**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**) Currently all SNS cases have annual follow up in secondary care and this would be the same for the Axonics device. (**NT**) Usually annual check up with neuro-physicist or specialist nurse. GP follow-up would not be appropriate as most would have no familiarity with the technology. (**AA**)
34.	Sent 22/10/19-23/10/19 Responses received 27/10/19-29/10/19	**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**) Nil else (**NT**) The presence of more than one provider will enhance this treatment by encouraging innovation and safe-guarding patients should a provider chose to pull out

				of the market or unreasonably raise costs. While I have been very pleased with the existing Medtronic device, in all medical devices, plurality of provision (and competition) should be encouraged. (**AA**).
35.	4/11/19	**Manufacturer** Email exchange	Is it possible that any patients might have been co-enrolled into both the ARTISAN-SNM and RELAX-OAB studies?	No it is not possible. Enrollment in the ARTISAN study occurred before the RELAX study was completed and our patients could not be part of 2 studies at the same time.
36.	Sent 17/01/2020 Responses received 20/01/2020-21/01/2020	**Expert advisers** Q&A via email	1. In your practice, have you found any differences in the duration or frequency of visits in the testing phase for either Axonics (rechargeable) compared to non-rechargeable devices? 2. Is there any difference in the way the devices are tested during this phase? 3. Are there any differences in the implantation procedure between Axonics and non-rechargeable devices? Is either more complex, or lengthy?	1. YES. Frequency of visits during test phase may be higher then current Medtronic device as only able to set one programme on the temporary IPG, to send patient home with **(MP)** Have not implanted the device so cannot answer for certain but I don't believe there should be a difference in time. **(NT)** I have never implanted an Axonics device **(CH)** Currently we only use the Medtronic testing kit (PNE Procedure) as we feel, as a team, that there was currently no need to have two testing systems available at this stage. On complication of a successful PNE we then offer the patient the choice of Permanent Devices available **(NF)** 2. NO **(MP)** No difference, both devices have different platforms to look at usage but assessment of response would be the same (ie subjective and objective improvement) **(NT)** Not to my knowledge **(CH)** 3. NO **(MP)** No difference **(NT)** No – they appear to be very similar **(CH)** In regards to surgical technique for Permanent

				implantation there is little difference between Axonics and Medtronic systems. No more complex or time consuming at this stage. On programing the implant, this takes slightly longer but we feel this is more to do with our familiarity with the equipment and will in time improve **(NF)**

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:

20190913
Additional 1.pdf

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

20190930
Additional 2.pdf

NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

External Assessment Centre Report factual check

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

Please find enclosed the assessment report prepared for this assessment by the External Assessment Centre (EAC).

You are asked to check the assessment report from Cedar to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 12pm, **11 November 2019** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAC and when appropriate, will be amended in the EAC report. This table, including EAC responses will be presented to the Medical Technologies Advisory Committee and will subsequently be published on the NICE website with the Assessment report.

6 November 2019

NICE National Institute for Health and Care Excellence

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The EAC report states on page 18 that "although individuals appear to have been prospectively recruited, it is not clear whether consecutive recruitment was used to ensure inclusion of all eligible participants."	We would like to propose to remove this sentence.	Consecutive recruitment was used, and all eligible participants were included in the study. This can be confirmed by study investigators.	**Text in EAC report replaced with:** "Although individuals appear to have been prospectively recruited, study authors did not report whether this was consecutive. During fact checking, the company informed us that consecutive recruitment had been used, and that all eligible participants were included in these studies."

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The EAC report states on page 18 that "furthermore, study eligibility criteria lacked clarity. For example, RELAX-OAB excluded people with "Any significant medical condition that is likely to interfere with study procedures, device operation, or likely to confound	We would like to remove the following statement: "Given that this definition is open to interpretation, and that both studies were funded by the company, the risk of selection bias is relatively high".	While we acknowledge that this criteria may be perceived as lacking clarity, and we acknowledge that we did not provide a description of criteria that would be used in clinical practice to select patients for whom the technology would be most appropriate, this exclusion	**Text amended in EAC report as follows:** "The company did not provide a description of criteria that would be used in clinical practice to select patients for whom the technology would be most appropriate. Furthermore, study eligibility criteria lacked clarity. For example, RELAX-

evaluation of study endpoints" (Blok et al. 2017). Given that this definition is open to interpretation, and that both studies were funded by the company, the risk of selection bias is relatively high. The company did not provide a description of criteria that would be used in clinical practice to select patients for whom the technology would be most appropriate."		criteria was meant to exclude patients unable to operate the device since this is a contraindication per the Axonics regulatory labelling. More importantly, none of the subjects in the study were excluded due to this criteria.	OAB excluded people with "Any significant medical condition that is likely to interfere with study procedures, device operation, or likely to confound evaluation of study endpoints" (Blok et al. 2017). The EAC considered that this definition could be open to interpretation by site investigators, and could contribute to a relatively high risk of selection bias (especially given that both studies were funded by the company). During fact checking, the company informed us that none of the subjects in the study were excluded because of this criteria, which had been intended to exclude patients unable to operate the device."

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The report states on page 18 that the uptake of concomitant medication to treat the condition at baseline is inconsistent with the requirement that the population is refractory and	We would like to propose the following paragraph instead:" McCrery et al. (2019) report that 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, who most often has exhausted	Having failed 2 medications is the definition of refractory OAB in the US. Even though as experts stated it may not be typical that patients continue to take medications in the UK while on SNM therapy, the situation	**Amended text in EAC report as follows:** McCrery et al. (2019) report that 40 of 129 people (31%) were "taking a concomitant medication to treat the condition" at baseline. This is not typical of a refractory OAB

that if patients in the ARTISAN-SNM study were not entirely refractory then there is a possibility that the medication may have had an adjuvant effect.	medication options before being offered SNM. Expert advice in the UK indicates that those who have failed conservative management and pharmacological treatment would not usually continue to take associated medications. This may be more reflective of a US population where the refractory OAB population is defined as having tried and failed at least 2 medications. It should be noted however that if patients in the ARTISAN-SNM study were taking medications at baseline, then any upside at follow up visits is to be attributed to the Axonics SNM therapy, as the risk is for patients to stop their medication after they received the implant, thereby potentially reducing the magnitude of the efficacy recorded.	exists in real life practice. As noted by the EAC, this is mitigated by the inclusion criteria which requires "no changes to current regimen of medications that affect bladder function for at least 4 weeks" prior to baseline data collection. Any additional effect would be due only to Axonics, and the risk is that patients stop taking the drugs during the study thereby hurting the results. Additionally, a post-hoc subgroup analysis was conducted between subjects that took concomitant medications at baseline and subjects that did not take concomitant medications at baseline. There was no statistically significant difference in responder rate results between these sub-groups at any follow-up visit.	population in the UK, who most often have exhausted medication options before being offered SNM. Expert advice in the UK indicates that those who have failed conservative management and pharmacological treatment would not usually continue to take associated medications. This may be more reflective of a US population where the refractory OAB population is defined as having tried and failed at least 2 medications. Possible consequences of conducting the ARTISAN-SNM study in a population where some patients continued to take concomitant medication have been proposed as: • an adjuvant effect (improving overall effectiveness). This is mitigated by the inclusion criteria which requires "no changes to current regimen of medications that affect bladder function for at least 4 weeks" prior to baseline data collection. • patients cease taking medication during SNM treatment (reducing overall effectiveness). The company informed the EAC that a post-hoc subgroup analysis was

			conducted between subjects that took concomitant medications at baseline and subjects that did not take concomitant medications at baseline. There was no statistically significant difference in responder rate results between these sub-groups at any follow-up visit."

Issue 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Only 2 of 129 participants (2%) in the ARTISAN-SNM study were male; although urinary incontinence is more common in females, expert advisors estimate that the proportion of males undergoing SNM treatment would usually be around 20%.	Only 2 of 129 participants (2%) in the ARTISAN-SNM study were male, which is reflective of the UUI patient population. Expert advisors estimate that the proportion of males undergoing SNM treatment would usually be around 20%, which is reflected in the proportion of males enrolled in the RELAX study focused on OAB patients (25%).	While the EAC report statement is not inaccurate per se, it opposes the male proportion of the ARTISAN study, which enrolled UUI patients, to the general OAB population. UUI is a population predominantly female, where a 2% male portion is reflective of the UUI patient population. The RELAX study enrolled OAB patients, including both UUI and UF patients, and had a rate of males closer to 25%, which as stated by the experts is reflective of the OAB population.	**No change to EAC report.** We have not seen any evidence that 2% male is reflective of the UUI population. In other publications, the prevalence of UUI in the UK population has been reported as: • 12% of men; 19% of women (n=1762, age 68 years) (Tsui et al, 2018) • 12% of men; 29% of women (n=7500, age ≥40 years) (Coyne et al. 2012 referenced by Milsom et al. 2014) • 24% of men; 25% of women (n=5091, age ≥70 years) (Foley et al. 2012 referenced by Milsom et al. 2014).

Issue 5

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Patient histories vary with regard to prior treatment. In ARTISAN-SNM, 13% (12/129) had received botulinum toxin therapy; 13% (12/129) had undergone tibial nerve stimulation;	Patient histories vary with regard to prior treatment. In ARTISAN-SNM, 13% (17/129) had received botulinum toxin therapy; 13% (17/129) had undergone tibial nerve stimulation;	Correction made to numerator	**Accepted proposed amendment - statement updated in EAC report.**

Issue 6

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
It is stated on page 18 of the EAC report that: “It is not clear whether statistical analysis plans and outcome measures were all predefined before commencement of the studies. The EAC has not seen a published protocol for either study. Historic changes to online registration information for the ARTISAN-SNM study (ClinicalTrials.gov archive)	We would like to remove this statement.	This statement is not accurate. The ARTISAN-SNM study was an Investigational Device Exemption study designed for the purpose of obtaining FDA premarket approval. The SAP was pre- planned and reviewed by the FDA before	**Accepted proposed amendment - statement deleted from EAC report.**

suggests that outcome measures could have been selected after commencement of patient recruitment."		patient recruitment. It is available upon request. Outcome measures were selected before study start/ patient recruitment. The study record was created in clinicaltrials.gov after the study start, and it is possible that this is reflected in the historic changes.	

Issue 7

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
The EAC report states on page 19: "On the other hand, the RELAX-OAB study record did specify changes in the ICIQ-OABqol score as its primary outcome measure in advance of recruitment. But this record also indicates that multiple quality of life tools were administered (including SF-12,	We would like to remove the following sentences: "There is therefore a risk of reporting bias in both studies" (page 19); and "although there is a possibility that only the best results were reported by study authors." (page 27).	The study authors reported only results of the ICIQ-OABqol questionnaire in the manuscripts because it was the primary endpoint of the RELAX study, and because it is the only quality of life questionnaire specific to OAB, which is therefore the only one that expert physicians consider relevant for this patient	**The justification is reasonable, but the EAC statement is not inaccurate. As a compromise, we have amended the text as follows:** The RELAX-OAB online registration information specified changes in the ICIQ-OABqol score as its primary outcome measure in advance of recruitment. But this record also indicates that multiple quality of life

EQ-5D, and I-QoL). The results of these before-and-after comparisons do not appear to have been reported in any of the publications (the same is true of the 'healthcare utilisation' measure). There is therefore a risk of reporting bias in both studies.". It is also stated on page 27: "although there is a possibility that only the best results were reported by study authors."		population. Additional quality of life measures are not specific to OAB, and therefore the authors decided to exclude them from the manuscripts.	tools were administered (including SF-12, EQ-5D, and I-QoL). The results of these before-and-after comparisons do not appear to have been reported in any of the publications (the same is true of the 'healthcare utilisation' measure). There is a risk of reporting bias, although the company has clarified that the ICIQ-OABqol tool was of most direct relevance to the study population. On page 28: Removed text as suggested. Sentence now reads: "More reliable are the quality of life results which were based upon the ICIQ-OABqol validated questionnaires."

Issue 8

Description of factual inaccuracy	**Description of proposed amendment**	**Justification for amendment**	**EAC response**
Table 2 - ARTISAN-SNM study	ICIQ-OABqol score (mean increase) is <u>34 points ($p < 0.0001$).</u>	Corrections	**Accepted proposed amendment and corrected both numbers in EAC report.**

Lane et al,12 month results, unpublished conference abstract and poster. ICIQ-OABqol score (mean increase) is 35 points ($p < 0.0001$). Symptom reduction : 78% responders had a minimum of 75% reduction in the number of UUI episodes per day; 29% were dry.	Symptom reduction : 77% responders had a minimum of 75% reduction in the number of UUI episodes per day; 29% were dry.		

Issue 9

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 2 Page 21 20 device-related AEs occurred in 13/25 people.	20 device-related AEs occurred in 13/51 people.	Correction	**Accepted proposed amendment and corrected in EAC report.**

Issue 10

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
It is stated in the report on page 22 that the explantation rate at 2 years is as follows: n = 7/51 (14%): • Infection at incision site: 1 • Lack of efficacy: 4 • High impedances: 1 MRI scan: 1 (device had not yet been approved for MR scan). It is further reported on page 38: "This reports 7 explants at two years, however we have excluded 3 of these that were due to lack of efficacy in non-test responders. In normal practice these patient would not have received a full implant. The EAC have used 4/34 responders (11.8%) as a conservative rate calculation."	Sponsor would like to propose to state an explantation rate of 6% (2/34) throughout the report (on both page 22 and page 38).	All patients who received an implant were tracked for safety data in both RELAX and ARTISAN studies. However, for other outcomes, it makes sense to focus on the initial/test responders group instead of the full implanted cohort, to be able to compare with other studies and more importantly real life practice. Indeed, patients who did not respond to the initial test phase post-implant (initial failures) would not receive an implant in real life. Moreover, only 2 patients out of the 34 test responders were explanted at 2 years and not 4, per the EAC report statement. The first one was explanted due to insufficient therapy response and the second one was explanted due to high impedances (suspected lead fracture). Therefore, Sponsor would like to update the explantation rate to 6% (2	**No change to table 2 (page 22). Added to explanatory text (page 26) for clarification:** "Including test non-responders, devices were explanted from…". **On page 38 (discontinuation rates) have not been changed. The papers do not clarify which of these patients were responders, and therefore the EAC have used 4/34 which, as we stated is a conservative interpretation of the data.**

		patients out of 34 initial responders) throughout the report.	

Issue 11

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 2 RELAX OAB data Standard deviation (SD) used instead of standard error (SE) **12 months:** In people with UUI, leaks were reduced from average (± SD) of 8.3 (± 0.8) per day at baseline to 1.8 (± 0.5) per day (p < 0.0001). In people with UF, voids were reduced from average (± SD) of 14.3 (± 1.1) per day at baseline to 8.0 (± 0.47) per day p < 0.0001.	**12 months:** In people with UUI, leaks were reduced from average (± SE) of 8.3 (± 0.8) per day at baseline to 1.8 (± 0.5) per day (p < 0.0001). In people with UF, voids were reduced from average (± SE) of 14.3 (± 1.1) per day at baseline to 8.0 (± 0.47) per day p < 0.0001. Devices were explanted from 2 people between 6 and 12 months due to lack of efficacy. In therapy responders with UUI, mean leaks per day reduced from 8.3 (SE ± 0.8) at baseline to 1.7 (SE ± 0.5) at 2 years (80% reduction, p < 0.0001). In therapy responders with UF, mean voids per day reduced from 14.3 (SE ± 1.1) at	All Standard Deviations stated in this paragraph are in fact Standard Errors.	**Accepted. Corrected SD to SE in column header and made table contents more concise. Replacement of SD with SE also applies to 2-year results.** **Removed SD from abbreviation table (page 7).**

Devices were explanted from 2 people between 6 and 12 months due to lack of efficacy. In therapy responders with UUI, mean leaks per day reduced from 8.3 (SD ± 0.8) at baseline to 1.7 (SD ± 0.5) at 2 years (80% reduction, $p < 0.0001$). In therapy responders with UF, mean voids per day reduced from 14.3 (SD ± 1.1) at baseline to 7.3 (SD ± 0.4) at 2 years ($p < 0.0001$).	baseline to 7.3 (SE ± 0.4) at 2 years ($p < 0.0001$).		

Issue 12

Description of factual inaccuracy	**Description of proposed amendment**	**Justification for amendment**	**EAC response**
Table 2 only reports responder rates of the ARTISAN study for All implanted patients (ITT). Figure 1 reports for the ARTISAN study an 88%	We propose to present both the All implanted patients response rates and the Test Responders response rates in Table 2 for the ARTISAN and RELAX studies, for completeness.	It occurs to Sponsor that it may help compare results between studies and to real life practice to add the responder rate of the Test responders to Table 2, which is 95% at 3 months in the	**The EAC considers intention-to-treat (ITT) results to refer to the proportion of therapeutic responders at follow-up (numerator) divided by the total number of test responders**

responder rate at 3 months (which is the ITT rate of all implanted patients), but then reports the 95% and 94% responder rates of 6 months and 1 year respectively, which are the Test responders rates and not the ITT rates for this study. The ITT responder rate for Test responders at 3 months in the ARTISAN study is 95%.	We propose to present the Test responders response rates only for the RELAX and the ARTISAN studies on Figure 1, for consistency.	ARTISAN study. Moreover, Figure 1 reports for the ARTISAN study an 88% responder rate at 3 months (which is the ITT rate of all implanted patients), but then reports the 95% and 94% responder rates of 6 months and 1 year respectively, which are the Test responders rates and not the ITT rates for this study. It may bring clarity to present Test responder results only instead of ITT results, because the ITT definition varies between studies. The responder rate for initial responders at 3 months in the ARTISAN study is 95%.	**(denominator). Any individuals lost to follow-up are included within the denominator and assumed to be a treatment failure (conservative analysis).** **Effectiveness outcomes for "all test responders" are less relevant as they do not reflect the 'real world' situation (in which only those who responded to SNM in the first month would continue to be monitored). However in the text we have included the whole-population 116/129 at 6 months, because that was the stated primary outcome measure.** **The company is correct in highlighting that the 3-month ITT calculation should be 107/113 (95%) rather than 88% (whole population including test non-responders). We have corrected this error in Figure 1. On page 24 we have removed the 88% sentence, and replaced the reference to ITT with:** "Based on analysis of the whole UUI population, 116 of 129 people (89.9%) were reported to be therapy responders at 6 months."

			Table 2 has been updated to report ITT data (proportion of test responders only) rather than "all participants": "Of the initial UUI test responders (n=113), those who responded to therapy at: 3 months: 95% (n=107) 6 months: 95% (n=107; 95% CI 83, 95, p<0.0001) 12 months: 94% (n=106; 95% CI 83, 94, p<0.0001) Statistical significance findings refer to change from baseline."

Issue 13

Description of factual inaccuracy	**Description of proposed amendment**	**Justification for amendment**	**EAC response**
Page 24 Urinary frequency (average voids per day) in the ARTISAN-SNM UF patients reduced from 11.6 ± 0.3 at baseline to 8.6 ± 0.2 at 6 months (p<0.0001). In the RELAX-OAB UF patients, the mean (± SD) voids per day were 14.3 ± 1.1 at baseline,	Urinary frequency (average voids per day) in the ARTISAN-SNM UF patients reduced from 11.6 ± 0.3 at baseline to 8.7 ± 0.2 at 6 months (p<0.0001). In the RELAX-OAB UF patients, the mean (± SD) voids per day were 14.3 ± 1.1 at baseline, reducing to 8. ± 0.5 by 1 year (p<0.0001	Correction	**Agreed and corrected on page 25:** **Corrected 8.6 to 8.7.** **Corrected 8.5 to 8.0.** **Also corrected SD to SE.**

reducing to 8.5 ± 0.5 by 1 year (p<0.0001			

Issue 14

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
It is stated on page 25 that results are "simply described as a 'significant improvement' (which may refer to clinical significance, rather than statistical significance)."	We propose to remove this statement.	Results of the ICIQ-OAB questionnaire were both clinically and statistically significant.	**Justification is confirmed in literature. Replaced with alternative text:** "simply described as a 'significant improvement' (referring to both clinical and statistical significance)."

Issue 15

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
It is stated in Table 3 that 3 months results of the ARTISAN study and 6 months results of the RELAX study for the ICIQ-OAB questionnaire are not reported.	Sponsor proposed to indicate that 3 months results of the ARTISAN study and 6 months results of the RELAX study for the ICIQ-OAB questionnaire are not available instead of not reported.	These numbers are reported in the form of graphs and published as such for simplification. They are simply not available in the public domain in the form of numbers so that they can be displayed in a table format. We believe this is different from for instance the 24	**In table 3, we have replaced "**NR**" (not reported) results at 3 months (ARTISAN-SNM) and 6 months (RELAX-OAB) with "**Significant improvement**". The company is correct in noting that these results are available in graphical form in the literature, accompanied by**

		months results of the ARTISAN study that are indeed not reported because not available yet.	**indications of statistical significance.**

Issue 16

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
It is stated in Table 3 that for the ARTISAN study at 1 year, the confidence interval for average change in the ICIQ-OAB questionnaire composite score is (30.2, 39.1) It is stated in Table 3 that the average change in the social score of the ICIQ-OAB questionnaire is +23	The confidence interval for the ICIQ-OABqol score improvement from baseline to 1 year is (29.9, 38.8) for the ARTISAN study. The average change in the social score of the ICIQ-OAB questionnaire is +22 and not +23.	Corrections	**The EAC had transposed CIs accurately based on the original company submission. We have updated as instructed. Confidence intervals cannot be verified from the available literature.** **The EAC agrees with the social score correction and has amended it accordingly.**

Issue 17

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
It is stated on page 27 of the report that "A possible exception is that the long-term incidence of surgical complications could be	We would like to change this sentence as follows: "A probable exception is that the long-term incidence of surgical complications could be reduced with rechargeable systems, as battery	As it is proven that replacement procedures are associated with adverse events, it is therefore expected that a reduction in	**No change to EAC report; not a factual inaccuracy.**

reduced with rechargeable systems, as battery replacement procedures are anticipated to be required less frequently."	replacement procedures are anticipated to be required less frequently."	replacement procedures would incur less adverse events.	

Issue 18

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 7.1.1 on page 29 states "The company designed their searches to include all economic studies of sacral nerve stimulation for overactive bladder. Although the company included 19 studies in their submission none of them are economic evaluations of Axonics and therefore do not meet the requirements of the scope and have been excluded by the EAC."	We suggest replacing by: "The company designed their searches to include all economic studies of sacral nerve stimulation for overactive bladder, in an effort to also capture comparator performance that might provide useful information to the committee. This yielded 19 studies that were included in the company submission. However, the EAC applied a more stringent definition to focus only on Axonics, and therefore excluded all but one of the identified evaluations."	The company's original submission stated in Table 1: "Note: Our search criteria, and inclusions/exclusions as listed in the appendix, were intentionally designed to include all economic studies of sacral nerve stimulation for overactive bladder. The reason was that we wanted to provide all evidence of SNM economics for the treatment of overactive bladder. If we were to have the search defined more strictly and would have limited to the scope narrowly to only identify studies that assess rechargeable vs. non-rechargeable, information that might be relevant to the	Text replaced with: ''The company designed their searches to capture all economic studies of sacral nerve stimulation for overactive bladder. This yielded 19 studies which were summarised in the economic submission and provided information about performance of the comparator device. None of these studies met the requirements of scope, however two contained relevant information for the economic model and are briefly reported on by the EAC.

		committee would not have been identified. It was therefore expected that the majority of studies would ultimately be labelled as 'not relevant' for the strict decision considered in our economic model." Furthermore, the EAC labelled the Noblett et al, 2017 study as 'directly applicable' and should therefore list it as included evidence. While it did not specifically compare the Axonics SNM System to the Interstim system, the study reported in this publication was clearly designed to compare rechargeable to non-rechargeable SNM technologies in the US, with only 1 existing product for each type: the Axonics rechargeable SNM system and the Interstim non-rechargeable SNM system.	

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Issue 19

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
It is stated on page 30 of the report that "Noblett *et al.* (2017) compares non-rechargeable InterStim device with rechargeable spinal cord stimulation systems (Eon Mini Rechargeable IPG, Nevro Senza SCS system)."	Sponsor proposes to remove this statement from the report.	The Noblett 2017 publication compared a rechargeable SNM technology to a non-rechargeable SNM technology. The mention of rechargeable Spinal Cord Stimulation (SCS) systems is used as an analogy to what could be the potential longevity of a rechargeable SNM system if it was available in the US, as the Axonics rechargeable SNM System was not approved in the US at the time of the study publication. Furthermore, the EAC, in Section 12.4, Appendix D, states the study is "Directly applicable" to the scope.	**Text replaced with:** "Noblett *et al.* (2017) compares a non-rechargeable with a rechargeable device. Assumptions about longevity of the neurostimulator devicse was based on the reported lifetime of the InterStim device for the non-rechargeable device and spinal cord stimulation systems (Eon Mini Rechargeable IPG, Nevro Senza SCS system) for the rechargeable device."

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Issue 20

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 40 states: “Lead migration, dislodgement or fracture: These rates are only applied at initial implant (index) procedure. The EAC does not agree that this is appropriate. The model published by Noblett at al. (2017) applied these at each replacement procedure. Consultation with clinical experts confirmed that adverse events with leads could occur throughout the lifetime of the device, often associated with injury or impact. The EAC have applied the rate at each cycle of the model in the revised EAC base case.	Eliminate sentence “The model published by Noblett at al. (2017) applied these at each replacement procedure.” as it is factually incorrect, per comment on the right, and our knowledge of the publication model’s structure.	The statement that the Noblett et al. (2017) model applied lead migration, dislodgment or fracture at each replacement procedure is incorrect. The Noblett et al, 2017 paper states: “In addition, patients could experience adverse events associated with the index procedure or subsequent replacement procedures. These included surgical site infection, surgical site pain, lead dislodgement or migration, or lead fracture.” This statement does not suggest that all of the adverse events occur during each replacement. The decision to not include these lead migration or lead fracture events in conjunction with device replacement cycles	As provided on page 40, EAC contacted the clinical experts who confirmed that adverse events with leads can occur throughout the lifetime of the device such as injury or impact. Our decision to apply this rate throughout the model was based on this information. The resulting impact on the model results was small. We have altered the text to: “The model published by Noblett at al. (2017) states that patients could experience adverse events associated with subsequent procedures, including lead dislodgement, migration or fracture. “

		was made at the recommendation of the clinical co-authors of the Noblett et al. paper, on the basis that a device replacement does not involve manipulation to the lead that could lead to dislodgment or fracture. Further, the clinical experts suggested that essentially all fracture events are based on incorrect lead placement post index that is fixed with a revision. There is no data to support the assumption that adverse events do occur at same frequency as in index implantation, if they occur at all.	

Issue 21

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
It is stated page 41 that "the Axonics device has additional resources including a charger and the tined lead extension. The tined lead extensions are	The Tined Lead extension is utilized to connect the Tined Lead to the External Neurostimulator in the context of a Tined Lead test phase prior to permanent implantation.	The Tined Lead extension is utilized to connect the Tined Lead to the External Neurostimulator in the context of a Tined Lead test phase prior to permanent implantation. It is not	The EAC comments were based on the use of component parts in the model. Table 7 correctly identified the components as they were used

only utilised for a lead revision or replacement."		used during lead revision or replacement procedures. We identified an error in the model that includes use of the Tined Lead extension and of the Trial Stimulator (for both the Interstim and the Axonics systems) for lead revision and lead replacement. This is incorrect. Only the Tined Lead and Tined Lead Introducer Kit should be used for lead revision and lead replacement. This error has only a marginal impact on the model outcomes (see revised Table 7 below).	in the submitted model, except for the test scenario. Based on the new information that has been submitted by the company, the EAC have updated the model and the associated results as an additional scenario Text updated to: "The Tined Lead extension is utilized to connect the Tined Lead to the External Neurostimulator during test phases prior to implant. Table 7 shows how components were costed in the submitted model. During fact check the company identified differences between the model and their expected use of components. The EAC have not changed the base case, but have added an additional scenario reflecting this information. There is only a small impact on the model outcomes."

Issue 22

<table>
<tr><th>Description of factual inaccuracy</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>EAC response</th></tr>
<tr>
<td>Table 7: Resources required during each procedure contains a number of inaccuracies</td>
<td>
<table>
<tr><th></th><th>Tined Lead (TL) Introducer Kit</th><th>Implanted Pulse Generator (IPG)</th><th>Tined leads (TL)</th><th>Charger</th><th>Percutaneous Nerve Evaluation (PNE) KIT</th><th>Trial Stimulator</th><th>Tined Leads (TL) extension</th><th>Patient remote control</th></tr>
<tr><td>Testing</td><td>✓</td><td></td><td>✓</td><td></td><td>✓</td><td>✓</td><td>●</td><td>✓</td></tr>
<tr><td>Initial implant procedure</td><td>✓</td><td>✓</td><td>✓</td><td>●</td><td></td><td></td><td></td><td>✓</td></tr>
<tr><td>Replacement due to infection</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Replacement due to pain</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Replacement due to battery depletion</td><td></td><td>✓</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Lead revision</td><td>✓</td><td></td><td>✓</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Lead replacement</td><td>✓</td><td></td><td>✓</td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
</td>
<td>Corrections</td>
<td>The table in the assessment report was correct in identifying the use of components in the submitted model, except in testing. The error in testing has been corrected.
Table added to section 7.3
Text added to 7.3: “During fact check the company identified differences between the model and their expected use of components. The EAC have added an additional scenario, with the EAC base case amended to reflect this information. Table 16 shows the updated resource use as listed by the company. In addition the EAC identified an error in the model that referenced a cell incorrectly for revisions due to pain. The correction of this error made less than £1 difference</td>
</tr>
</table>

Required replacement of Charger System at 7.5 years				●					
Required replacement of Patient Remote at 7.5 years								✓	
✓required for both devices; ●required for rechargeable device only									

to the outcome. Overall the update has only a small impact on the model outcomes."

Added to table 15:

Post Fact check update on resources following additional information from company (table 16) and error correction.	£19,695	£26,041	-£**6,345**

Issue 23

Description of factual inaccuracy	**Description of proposed amendment**	**Justification for amendment**	**EAC response**
The report states page 12 that: "the EAC considers that the company's search strategy was weak and lacked defined medical subject headings. The search approach was very limited with only one database being searched; details are provided in appendix A.	We would like to add a statement that the new search conducted by the EAC did not lead to the identification of additional studies or publications relevant to the scope.	While we understand that our search strategy for clinical literature did not meet all the required criteria set by NICE, and we apologize that the EAC had to conduct their own search for publications, we would like to	**Accepted this justification and added text as requested:** "The new search conducted by the EAC did not lead to the identification of additional studies or publications relevant to the scope."

Therefore, to ensure that all relevant evidence had been identified, the EAC conducted their own systematic search, to include periods from 1st January 2010 until 21st August 2019. Ten bibliographic databases and 2 clinical trial registries were searched using a range of free text terms and (where appropriate) subject headings. The MHRA's medical device alerts and field safety notices were searched for adverse events."		detail the reasons behind our more limited search strategy: - We knew all the clinical literature specific and relevant to the Sponsor technology and to the Comparator technology to be limited to the publications we reported in our submission. This was made possible through prior and very recent searches as well as a highly active knowledge of the space. We do not believe that the search conducted by the EAC led to the identification of additional studies. - We knew that no adverse events were reported to the MHRA at the time of our submission - The scope of this guidance was made available 2 weeks prior to our submission deadline instead of 6 weeks, we therefore needed to prioritize and selected to	

		focus our work on other sections of the submission given our knowledge of what the search results would be.	

Issue 24

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Appendix E: It is stated that the EAC is “slightly confused by these two results. When the discontinued rate is made 100% for Axonics its price increases, when done for comparator it decreases significantly (which is what I had expected to happen with Axonics)”	We suggest the EAC eliminate this comment and replace by “As expected” upon applying the calculation the way described on the right. The EAC should also update the resulting values for Axonics cost, Comparator Cost, and Cost difference for this extreme scenario.	The model was encoded to properly handle therapy adoption rates in ranges that would be reasonably expected. It functions properly if these bounds are not exceeded. The EAC, in their stress test, entered 100% discontinuation rate in each of the first four calculation cycles. This leads to an artefact where the cumulative discontinuation rate fluctuates between a positive and negative percentage between each of the first four cycles. In turn, this leads to the observed values. To properly test the extreme scenario of 100% therapy	**Text has been amended to:** These results are due to the incorrect calculation of the cumulative discontinuation rate. The effect is that there are large negative numbers of patients with the implant, and replacement results in a negative cost. Thus in this situation the treatment gets cheaper over time. This is obviously a modelling artefact, not a possible real situation. There is less impact on the axonics arm, as there is only one replacement procedure. As there are more patients with the implant, over time, then the cost of adverse events also increases. With the EAC corrections, the impact is greatly reduced

		discontinuation in the first cycle, the EAC is advised to manually set the value of “Therapy discontinuation (cumulative)” in the “Projections – Cost” tab to 100% for cycle 0.25 years and any following cycles. The costs are then accurately calculated, with the non-rechargeable SNM technology incurring lower total cost, as expected.	

Issue 25

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Appendix E: Comments in second and fifth scenario refer to “price” as opposed to “cost”	Replace “price” by “cost” in both instances	The EAC intends to discuss costs here, not prices	These have been corrected to “cost”

Issue 26

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 12.4 Appendix D states “The cost in base case results were presented as not discounted”	We propose to eliminate this statement because it is incorrect.	The manuscript, in the Results section, states “At base-case assumptions, discounted 15-year costs for the non-rechargeable and rechargeable strategies were $64,111 and $36,990, respectively, resulting in total cost savings for the rechargeable strategy of $27,121 (Table II).” Additionally, a non-discounted scenario is presented.	The statement is removed.