Application Type: New Listing – Prostheses Devices (System)

Application Fee: $1200

Application Type:	NEW	**Status:**	Submitted
Reference Number:	s47G	**Last Updated:**	03/05/2023 14:15, s47F
Product / System:	InterStim™ X System		

Application Contacts

Primary Contact:	s47F	
Phone Number #1:	Office	s47F
Phone Number #2:		
Email:	s47F	
Secondary Contact:		
Phone Number #1:	Office	s47F
Phone Number #2:		
Email:	rs.mdtreimbursement@medtronic.com	

The list of added products for this application

Product#	Product Name
1	InterStim X System – Neurostimulator
2	s22

Product Details - Product #1

Product Type:*	PROSTHESIS_DEVICE
Product Name:*	InterStim X System – Neurostimulator
Description:*	Recharge-free implantable neurostimulator
Size(s):*	One size only
Catalogue Number(s):*	97800
Proposed Benefit:*	s47G

Grouping

Category:	05 - Urogenital
Sub Category:	05.07 - Sacral Neuromodulation
Group:	05.07.01 - Primary Cell Pulse Generator (non-rechargeable)
Sub Group:	Extended Battery Life
Suffix(es):	
Group Benefit:	Not available for new grouping

ARTG Number(s)

ARTG ID Number	Sponsor Name	ARTG Entry Name	Class
No ARTG Numbers			

Alternatively, tick here if you have applied to include your device on the ARTG

☐ ARTG ID Number is pending

ARTG Application Number:*	DV-2023-DA-01233-1
TGA Application Date:*	18/01/2023

Comparator(s)

☐ Comparator is an existing item on the prosthesis list

☐ Comparator is not an existing item on the prosthesis list

Billing Code:	MC755
Comparator Product Name:	InterStim II Neurostimulator
Comparator Product Grouping:	05 - Urogenital
Sub Category:	05.07 - Sacral Neuromodulation
Group:	05.07.01 - Primary Cell Pulse Generator (non-rechargeable)
Sub Group:	
Suffix(es):	
Comparator Selection Explanation:*	Equivalent neurostimulator designed to deliver stimulation as part of a neurostimulation system for sacral neuromodulation therapy.

☐ Main Comparator for Product

Evidence, Benefit and Economic Information for New Grouping

Product Name:	InterStim X System – Neurostimulator
Category:	05 - Urogenital
Sub Category:	05.07 - Sacral Neuromodulation
Group:	05.07.01 - Primary Cell Pulse Generator (non-rechargeable)
Sub Group:	Extended Battery Life
Suffix(es):	
Proposed Benefit:	s47G
Benefit Rationale:	s47G 10% of the cost of the replacement procedure should be attributed to the additional benefit uplift based on extended device warranty.
Main Comparator:	InterStim II Neurostimulator
Benefit/Cost:	$9072

Clinical Outcomes

Please identify the quantifiable or measurable clinical outcomes delivered by your product, compared with the comparator(s). Refer to the measurable and/or quantifiable factors relating to patient otucomes, such as recovery time, failure rates, complications, life expectancy:*

Please see attached supporting document "Medtronic Value Summary for InterStim X""

Cost Comparison

Please provide details of measurable evidence of any cost savings achieved through the use of the product:*

Please see attached supporting document "Medtronic Value Summary for InterStim X""

Product Utilisation

If your product is sold in Australia and/or any other country, please provide utilisation and price details below:

Country	Utilisation per year	Cost (in local currency)
No utilisation		

What is the projected utilisation of the product over the first two years of listing on the Prostheses List?

s47G

What is the basis for the projection?

Assuming a 100% substitution from the main comparator InterStim II Neurostimulator (Billing Code MC755)

Will the use of this product replace the use of another product? *

- Yes
- No

Please advise which product will be replaced by the use of this product:*

InterStim II Neurostimulator (Billing Code MC755)

Other Information

Is there any other information you can provide to support your proposed benefits for your product?

Comparative Clinical Effectiveness

Overseas Status

Has authority been given to sell this product / product system in any other country? *

- Yes
- No
- Unknown / Not available

Please provide information about the approvals*

CE mark, FDA, Health Canada

Has the product/product system been sold or being sold, under any other name in any country? *

- [ ] Yes
- [ ] No

Comparative Clinical Effectiveness

Please explain how the clinical effectiveness and cost effectiveness of your product/product system compares with the comparator(s). Please refer to the clinical evidence you have provided above to support your application*

Please see attachments "Medtronic Value Summary for InterStim X"

s22

ARTG Number(s)

ARTG ID Number	Sponsor Name	ARTG Entry Name	Class
No ARTG Numbers			

Alternatively, tick here if you have applied to include your device on the ARTG

- [ ] ARTG ID Number is pending

ARTG Application Number:*	s22
TGA Application Date:*	

s22

Attachments

File Name	Type	Description / Study Name & Journal Reference
Limited Warranty Statement ANZ_Interstim X.pdf	Product System - Supporting Literature	Warranty Statement
InterStimX - product catalogue.pdf	Product System - Product Image	Product Brochure

s47G

Medtronic Value Summary for Interstim X [FINAL].pdf	Product#1 InterStim X System – Neuros... - Supporting Document	Value Summary

Submit Application

I declare that all information provided in this application is true and correct. I agree to pay the application fee listed above. *

PLMS Extract s47G

3/10/2023	Application Recommended	The Medical Device and Human Tissue Advisory Committee (MDHTAC) considered the application and noted the device is sacral neurostimulator with a non-rechargeable but extended life battery, and the sponsor applied to list the device in group 05.07.01 -Urogenital – Sacral Neuromodulation – Primary Cell Pulse Generator (non-rechargeable), in the New sub-group Extended Battery Life, with benefit s47G . s47C [redacted] s47G . MDHTAC recommended the device is suitable for listing in group 05.07.01 - Urogenital - Sacral Neuromodulation - Primary Cell Pulse Generator (no-rechargeable) and new subgroup Extended Battery Life (05.07.01.01), with benefit s47G .
14/08/2023	Awaiting PLAC	General Surgery Expert Clinical Advisory Group (GSECAG) assessed the application and noted that the device has a non-rechargeable battery but with the extended life, and the sponsor applied to list it in the new sub-group Extended Battery Life with the benefit s47G that is the same as the benefit payable for group 05.07.05 for the Sacral Neuromodulation rechargeable neurostimulators. s47C [redacted]. It was noted that the benefit for the re-rechargeable neurostimulators was estimated based on the battery life of 10 year, and according to the manufacturer's warranty statements the expected life of the subject device (Medtronic Interstim™ X Neurostimulator) is also 10 years. Members recommended the subject device is suitable for listing in the new sub-group 05.07.01.01 – Urogenital – Sacral Neuromodulation – Primary Cell Pulse Generator (non-rechargeable) - Extended Battery Life, with benefit s47G

30/05/2023	Further Information Required	This message is to acknowledge receipt of your application and ask you to provide the information that has not been provided and is required to inform the assessment. This missing information includes: The pulse generator in the application is a Class III device, but no clinical evidence has been provided to assess comparative clinical effectiveness. Clinical outcomes data on the device in the application is required for assessment. Please attach peer-reviewed papers of independent studies with clinical outcomes data on the device in the application. The information stated above is required to be submitted in PLMS by no later than Tuesday 6 June 2023. If you have any questions, email them to: Prostheses@health.gov.au.

s22

From: s47F
Sent: Tuesday, 6 June 2023 4:50 PM
To: Prostheses/Health
Cc: rs.mdtreimbursement@medtronic.com
Subject: RE: [EXTERNAL] PLMS - Application Status of InterStim X System – Neurostimulator in InterStim™ X System s47G has been updated to FURTHER INFORMATION REQUIRED [SEC=OFFICIAL] [SEC=OFFICIAL]
Attachments: tjandra2008.pdf; Zhang 2019.pdf; Siegel 2015.pdf; s47G

Follow Up Flag: Follow up
Flag Status: Flagged

Categories: URO

Dear Prostheses Section,
In response to your below query, InterStim X was developed from the predicate InterStim II and is considered clinically equivalent. InterStim X incorporates modifications to its battery technology, resulting in an extended battery life s47G This advancement contributes to cost savings for the Australian healthcare system by reducing the need for replacement surgeries.
s47G

Regards,
s47F
Reimbursement Analyst
Healthcare Economics, Health Policy & Reimbursement, ANZ
Medtronic
Medtronic Australasia Pty Ltd
s47F
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Office +s47F | Mobile s47F
s47F
medtronic.com | Facebook | LinkedIn | Twitter | YouTube

Medtronic Australasia acknowledges the ancestors and traditional custodians of the land on which our offices stand and pay respect to Elders past and present.

Please note that I only check my emails a few times each day. If your matter is urgent, kindly give me a call.

From: Prostheses@health.gov.au
Sent: Tuesday, 30 May 2023 1:09 PM
To: s47F ; RS MDT Reimbursement
Subject: [EXTERNAL] PLMS - Application Status of InterStim X System – Neurostimulator in InterStim™ X System s47G has been updated to FURTHER INFORMATION REQUIRED [SEC=OFFICIAL] [SEC=OFFICIAL]

The status of InterStim X System – Neurostimulator in your Application NEW: InterStim™ X System (s47G) has been updated.

New Status: FURTHER INFORMATION REQUIRED
Previous Status: SUBMITTED
Date/Time: 30/05/2023 13:09:00
Updated by: HEALTH
Comment: This message is to acknowledge receipt of your application and ask you to provide the information that has not been provided and is required to inform the assessment. This missing information includes: The pulse generator in the application is a Class III device, but no clinical evidence has been provided to assess comparative clinical effectiveness. Clinical outcomes data on the device in the application is required for assessment. Please attach peer-reviewed papers of independent studies with clinical outcomes data on the device in the application. The information stated above is required to be submitted in PLMS by no later than Tuesday 6 June 2023. If you have any questions, email them to: Prostheses@health.gov.au.

Please reply to this email or contact the Department of Health at Prostheses@health.gov.au if you require further information.

Neurourology and Urodynamics 34:224–230 (2015)

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

Steven Siegel,[1] Karen Noblett,[2*] Jeffrey Mangel,[3] Tomas L. Griebling,[4] Suzette E. Sutherland,[5] Erin T. Bird,[6] Craig Comiter,[7] Daniel Culkin,[8] Jason Bennett,[9] Samuel Zylstra,[10] Kellie Chase Berg,[11] Fangyu Kan,[11] and Christopher P. Irwin[11]

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[5]Metro Urology, Plymouth, Minnesota
[6]Scott and White Healthcare, Temple, Texas
[7]Stanford University, Stanford, California
[8]University of Oklahoma HSC, Oklahoma City, Oklahoma
[9]Female Pelvic Medicine, Grand Rapids, Michigan
[10]Milford Regional Medical Center, Whitinsville, Massachusetts
[11]Medtronic, Minneapolis, Minnesota

Aims: This prospective, randomized, multicenter trial evaluated the 6-month success rate of sacral neuromodulation (SNM) with InterStim® Therapy versus standard medical therapy (SMT) for overactive bladder (OAB). **Methods:** Enrolled subjects discontinued OAB medications prior to and during baseline data collection and were randomized 1:1 to SNM or SMT. Subjects had bothersome symptoms of overactive bladder (OAB) including urinary urge incontinence (≥2 leaks/72 hr) and/or urgency-frequency (≥8 voids/day). Subjects failed at least one anticholinergic medication, and had at least one medication not yet attempted. The primary objective was to compare OAB therapeutic success rate at 6 months between SNM and SMT. **Results:** Overall, 147 subjects were randomized (70 to SNM and 77 to SMT); 93% were female and mean age was 58. The primary intent to treat analysis showed OAB therapeutic success was significantly greater in the SNM group (61%) than the SMT group (42%; $P = 0.02$). In the as treated analysis, OAB therapeutic success was 76% for SNM and 49% for SMT ($P = 0.002$). The SNM group showed significant improvements in quality of life versus the SMT group (all $P < 0.001$) and 86% of SNM subjects reported improved or greatly improved urinary symptom interference score at 6 months, compared to 44% for SMT subjects. The device-related adverse event rate was 30.5% and the medication-related adverse event rate was 27.3%. **Conclusions:** This study demonstrates superior objective and subjective success of SNM compared to SMT. SNM is shown to be a safe and effective treatment for OAB patients with mild to moderate symptoms. *Neurourol. Urodynam. 34:224–230, 2015.* © 2014 Wiley Periodicals, Inc.

Key words: anticholinergic; overactive bladder; sacral neuromodulation; urgency frequency; urinary incontinence

INTRODUCTION

Overactive bladder (OAB) is an umbrella term that covers several lower urinary tract symptoms including urinary urgency, frequency, nocturia, and urgency incontinence.[1] A recent study estimated that one in three adults over 40 suffers from moderate to severe OAB with the prevalence increasing with age.[2] Although not life threatening, it does have a significant impact in most domains of quality of life.[3] Additionally, specific medical conditions are associated with OAB, including a higher incidence of urinary tract and perineal skin infections, clinical depression, as well as a higher risk of falls and hip fractures, increasing by 28% and 32%, respectively.[4] Recently the American Urological Association published treatment guidelines for OAB.[5] This is a three-tiered algorithm that places behavioral therapy in the first tier, pharmacological therapy in the second tier and sacral neuromodulation (SNM) as the only recommended therapy in the third tier. However, persistence and adherence with pharmacological therapy are suboptimal. A recent study indicated that over 50% of subjects with OAB discontinued pharmacotherapy (regardless of the particular agent) due to lack of efficacy or intolerable side effects at 12 months.[6]

SNM has been FDA-approved for the treatment of urgency incontinence (UI) since 1997, for urgency-frequency (UF) since 1999, and is recognized an effective treatment for refractory

Medtronic, Inc., sponsored this study in full.
Dirk De Ridder led the peer-review process as the Associate Editor responsible for the paper.
Clinical trial identifier: InSite for Overactive Bladder; NCT00547378
*Correspondence to: Karen Noblett, M.D., University of California, Irvine, CA.
E-mail: knoblett@uci.edu
Received 21 August 2013; Accepted 26 November 2013
Published online 10 January 2014 in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/nau.22544

TABLE I. Inclusion and Exclusion Criteria

Inclusion criteria
Diagnosis of OAB as demonstrated on a 3-day voiding diary demonstrating greater than or equal to 8 voids/day and/or by having a minimum of two involuntary leaking episodes in 72 hr
Male or female and 18 years of age or older
Failed or are not a candidate for more conservative treatment (e.g., pelvic floor training, biofeedback, behavioral modification)
Failed or could not tolerate at least one anticholinergic or antimuscarinic medication AND have at least one anticholinergic or antimuscarinic medication not yet attempted
On current regimen of OAB medications or have not been on any OAB medications, for at least 4 weeks prior to beginning the baseline voiding diary
Exclusion criteria
Severe or uncontrolled diabetes or diabetes with peripheral nerve involvement.
Concomitant medical conditions which would limit the success of the study procedure
Skin, orthopedic or neurologic anatomical limitations that could prevent successful placement of an electrode
Neurological diseases such as multiple sclerosis, clinically significant peripheral neuropathy or complete spinal cord injury (e.g., paraplegia)
Knowledge of planned MRIs, diathermy, microwave exposure, high output ultrasonic exposure, or RF energy exposure
Urinary tract mechanical obstruction such as benign prostatic hypertrophy, cancer, or urethral stricture
Symptomatic urinary tract infection
Implantable neurostimulators, pacemakers, or defibrillators
Primary stress incontinence or mixed incontinence where the stress component overrides the urge component
Treatment of urinary symptoms with botulinum toxin therapy in the past 12 months
Life expectancy of less than 1 year
Pregnant or planning to become pregnant or are a woman of child-bearing potential who is not using a medically acceptable method of birth control

OAB.[7,8] The only commercially available form of SNM is InterStim® (Medtronic, Minneapolis, MN). InterStim functions by delivering mild electrical impulses to the sacral nerve roots via an implanted neurostimulator and lead typically placed adjacent to the 3rd sacral nerve root, which allows for communication with the neural system controlling effector organs (bladder) and muscles (sphincters) innervated by the sacral nerves. Original studies demonstrating the effectiveness of SNM used an older, more invasive surgical approach, and while significant benefit was achieved, randomized studies enrolling a contemporary subject population utilizing newer minimally invasive techniques, including the tined lead, are scarce.

The InSite trial is a prospective, multicenter, FDA-mandated post-approval study to evaluate safety of the tined lead at 5 years. The study included an effectiveness analysis that compared OAB therapeutic success in a subset of subjects randomized to SNM or standard medical therapy (SMT) of anticholinergic or antimuscarinic medication and followed for 6 months. The primary hypothesis of the randomized portion was that SNM is superior to SMT in this population where at least one medication had been tried, but other pharmacologic agents were still available. As this is an ongoing trial, the quality and duration of treatment benefit and safety in this less severe study population will continue to be evaluated.

MATERIALS AND METHODS

Study Design and Procedures

Enrolled subjects met all inclusion and none of the exclusion criteria (Table I). The research protocol was approved by institutional review boards and participants gave written informed consent prior to initiation into the study. Previous treatment failure consisted of inadequate symptom control and/or unacceptable adverse drug events with at least one anticholinergic medication.

After enrollment, subjects completed baseline electronic diary information and questionnaires and were randomized to SNM or SMT in a 1:1 ratio. All subjects were required to discontinue OAB medications for 4 days prior to their initial voiding diary. Subjects randomized to SNM with full system implant were required to remain off OAB medications from test stimulation through 6 months. Subjects randomized to SMT started the next recommended antimuscarinic medication per physician discretion, or restarted the discontinued medication.

Subjects randomized to SNM underwent a staged procedure using the InterStim® Therapy system[a] requiring a 14-day test stimulation period. If successful test stimulation was demonstrated [≥50% improvement from baseline in average leaks/day or voids/day or a return to normal voiding (<8 voids/day)] based on voiding diary parameters, the neurostimulator was implanted. Details of the implant procedure have been previously reported.[9] Subjects who failed to show a successful response during test stimulation were allowed to repeat a test stimulation procedure on one additional occasion. Subjects randomized to SNM who never received a full system implant continued follow up through the 6-month visit and were analyzed in the SNM group (intent to treat analysis).

Outcomes

The primary outcome measure, OAB therapeutic success, was determined using voiding diaries collected at the 6-month follow-up visit. To be considered a success, subjects with both UI and UF had to demonstrate either a ≥50% improvement in average leaks/day or voids/day from baseline or a return to normal voiding frequency (<8 voids/day). A subject was only counted once if s/he met the definition of success for both voids and leaks. A Clinical Events Committee reviewed all adverse events.

Additional a priori objectives were to compare QOL measures between groups at 6 months using the following validated questionnaires: International Consultation on Incontinence Modular Questionnaire (ICIQ)-OABqol including a single item on urinary symptom interference; ICIQ—Male/Female Lower Urinary Tract Symptoms-Sex[10]; Beck Depression Inventory II; and a Visual Analog Scale for pelvic pain.

Sample Size and Statistical Analyses

A total of 94 subjects (47 per group) were required to provide 80% power for a two-tailed, alpha = 0.05 comparison of

[a] Neurostimulator models 3023 and 3058. Lead models 3093 and 3889.

6-month OAB therapeutic success rates, assuming 53% for SNM and 23% for SMT. Success rates were estimated from previous studies with adjustment for a fraction of SNM subjects who did not receive a system implant. In order to meet the required 94 subjects needed to complete follow-up, 132 subjects were planned to be randomized to account for attrition and ensure the requirement could be sufficiently met. All subjects were analyzed in the group to which they were assigned, regardless of treatment received. Subjects who failed to complete follow-up were assumed to be treatment failures. A sensitivity analysis based on the treatment that subjects received (hereafter, "as treated") was also conducted on the primary analysis, and only included those subjects with both baseline and follow-up measurements. All other efficacy analyses are also reported similarly. Therapeutic success results are reported as sample proportions. QOL results were calculated by subtracting baseline from 6 months. Published scoring criteria[11] were used whenever possible. Overall assessment on interference change is categorized as worsened, no change, improved, and greatly improved. Safety was evaluated through adverse events and statistical comparisons were made between SNM subjects with full system implant and SMT subjects without an implant.

Between group differences were tested using Fisher's Exact test for categorical variables and Wilcoxon's rank sum test for continuous or ordinal variables. All statistical tests were examined for significance at the 0.05 level, with no adjustments for multiple testing. SAS software (version 9.2, SAS Institute, Cary, NC) was used for all analyses.

RESULTS

Between November 2007 and June 2010, 243 subjects were enrolled from 38 sites; 147 were randomized, 70 were allocated

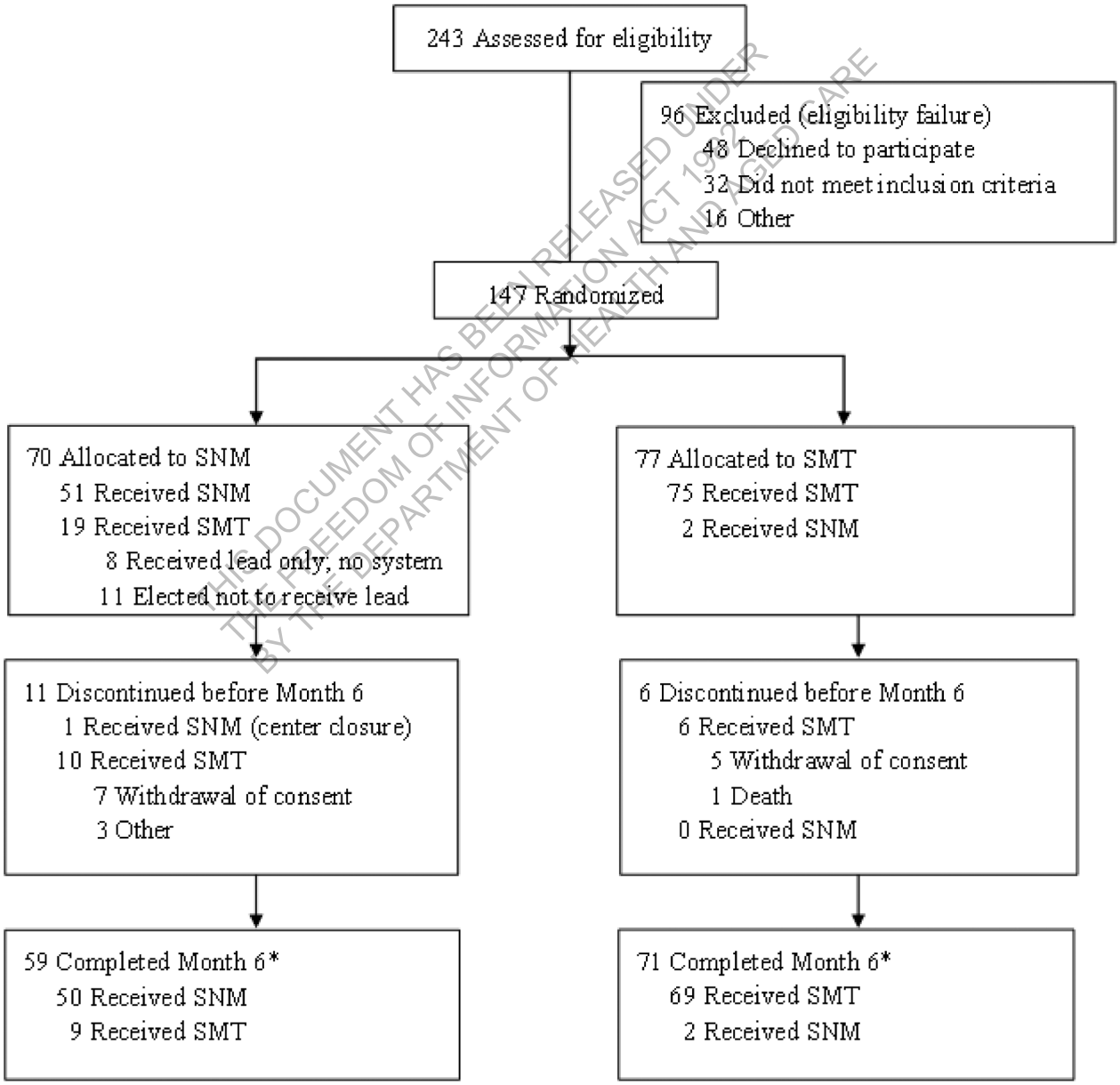

Fig. 1. Subject flow diagram. *Not all subjects who completed Month 6 completed all required assessments

to SNM and 77 to SMT (Fig. 1). Study outcome data remained blinded until follow-up of the randomized subjects was completed. There were no significant differences between the groups in demographics, baseline assessments, or medical history (Table II). Subjects tried a median of two OAB medications prior to study enrollment. Of the 70 subjects randomized to SNM, 59 underwent test stimulation, and 51 (86%) received a full system implant.

Nearly all SMT subjects (96.1%) used OAB medication between randomization and six months and 70% used medications on at least 80% of the days during the 6-month period. In many cases, subjects used more than one medication during the follow-up period. Only two (3.9%) SNM subjects with full system implant used medications between test stimulation and 6 months.

Primary Outcome

For the primary analysis using ITT (Fig. 2A), the OAB therapeutic success rate at 6 months was 61% for SNM compared to 42% for SMT ($P = 0.02$). Similar findings were demonstrated in the as treated analysis, with OAB success rates of 76% for SNM and 49% for SMT ($P = 0.002$). These data support the primary hypothesis that SNM is superior to SMT in the treatment of OAB. For subjects with UI at baseline, 71% of SNM and 47% of SMT subjects demonstrated therapeutic success ($P = 0.03$). Complete continence was almost doubled in the SNM group compared to the SMT group (39% vs. 21%, respectively, $P = 0.06$; Fig. 2B). For subjects with UF at baseline, normal voiding patterns (<8 voids/day) were achieved in 61% of SNM subjects and 37% of SMT subjects ($P = 0.04$; Fig. 2C).

TABLE II. Baseline Demographics and Medical History*

Demographic	SNM (n = 70)	SMT (n = 77)
Gender		
Female	66 (94%)	71 (92%)
Male	4 (6%)	6 (8%)
Race		
White	61 (87%)	70 (91%)
Black	7 (10%)	7 (9%)
Asian/White	1 (1%)	0 (0%)
Other	1 (1%)	0 (0%)
Primary pre-study diagnosis		
Urge incontinence	44 (63%)	46 (60%)
Urgency-frequency	26 (37%)	31 (40%)
OAB qualification per study diary		
Urinary incontinence only	25 (36%)	27 (35%)
Urgency frequency only	19 (27%)	16 (21%)
Both	26 (37%)	34 (44%)
Secondary diagnoses		
Stress incontinence	36 (51%)	32 (42%)
Urinary frequency	29 (41%)	29 (38%)
Urinary urge incontinence	17 (24%)	23 (30%)
Interstitial cystitis	4 (6%)	9 (12%)
Retention	0 (0%)	3 (4%)
Pelvic pain	1 (1%)	2 (3%)
None	8 (11%)	8 (10%)
Number of previous medications		
1	20 (29%)	17 (22%)
2	21 (30%)	28 (36%)
3	14 (20%)	14 (18%)
4–7	15 (21%)	18 (23%)
Age at consent (yrs)	60.4 ± 14.4	57.1 ± 15.3
Years since diagnosis	9.2 ± 10.5	7.4 ± 7.1
Baseline leaks/day	2.4 ± 1.7 (n = 51)	2.7 ± 1.9 (n = 61)
Pads replaced/day	1.1 ± 1.1 (n = 51)	1.5 ± 1.5 (n = 61)
Urgency of leaks[a]	3.0 ± 0.8 (n = 51)	3.1 ± 0.8 (n = 61)
Baseline voids/day	11.2 ± 2.9 (n = 45)	11.9 ± 4.3 (n = 50)
Void volume/void (ml)[b]	157.2 ± 77.0 (n = 37)	159.2 ± 87.9 (n = 36)
Urgency of voids[a]	2.9 ± 0.4 (n = 45)	3.0 ± 0.5 (n = 50)

*Plus-minus values are mean ± SD. None of the characteristics differed significantly between groups.
[a]Urgency of each leak and void was rated on the following scale: 1 = no urgency, 2 = mild, 3 = moderate, 4 = severe.
[b]Void volume was only summarized for subjects reporting volume on at least 50% of their voids.

Additional Outcomes

Changes from baseline in OAB QOL between groups showed greater improvement in SNM compared to SMT (all $P < 0.001$, Fig. 3A). Eighty-six percent of SNM subjects reported improved or greatly improved urinary symptom interference score at 6 months, compared to 44% for SMT subjects (Fig. 3B). SNM females had a greater improvement in sexual function than SMT ($P < 0.05$). Additionally, SNM demonstrated a greater improvement in depression compared to SMT ($P = 0.01$).

Safety was evaluated through adverse event (AE) analysis. There were no unanticipated adverse device effects. Device-related AEs (related to surgery, therapy, device, or implant site) occurred in 30.5% (18/59) of subjects with a lead implant and none were serious. OAB medication-related events occurred in 27.3% (21/77) of SMT subjects and none were serious. Statistical comparisons were made between 51 SNM subjects with full system implant and 75 SMT subjects without an implant. The SNM group had a higher number of urinary tract infections compared to the SMT group ($P = 0.01$); about one third of the events occurred prior to lead implant in the SNM group. The serious AE rates for both groups were not significantly different and were low, 9.8% (4/51) in SNM and 5.3% (4/75) in SMT. One SMT subject died during the study due to an unrelated cerebrovascular aneurysm. The most common device-related AE's in SNM subjects were undesirable change in stimulation 10.2% (6/59), implant site pain 8.5% (5/59), lead migration/dislodgment 3.4% (2/59), and implant site infection 3.4% (2/59). The three most common medication-related AEs in SMT subjects were constipation 9.1% (7/77), drug toxicity 6.5% (5/77), and dry mouth 5.2% (4/77). For the 51 SNM subjects with full system implant, the 6-month post-implant surgical intervention rate was 3.9% (2/51).

DISCUSSION

This prospective, multi-center, randomized clinical trial provides level-one evidence for the objective and subjective superiority of SNM over SMT among refractory patients with mild to moderate symptoms of OAB. It also confirms the safety of currently used techniques for SNM. For the primary outcome, 61% of SNM subjects demonstrated therapeutic success at 6 months versus 42% of the SMT subjects using an intent to treat analysis ($P = 0.02$). The significant difference between success rates using this conservative analysis emphasizes the strength of the results. Predictably, therapeutic success was more robust in subjects actually receiving SNM versus SMT (76% response in the SNM group and 49% in the SMT group, $P = 0.002$, as treated analysis). The differences demonstrated between the as treated groups is a more realistic reflection of that expected in routine patient care. The rate of complete continence was nearly doubled in the SNM group (39% vs. 21%), and this trended towards statistical significance ($P = 0.06$).

In contrast to early InterStim publications, this study population had less severe OAB symptoms based on voiding diaries.[7,8,12] InSite subjects had a low mean number of baseline leaks/day (2.6) and voids/day (11.6), compared to the MDT-103

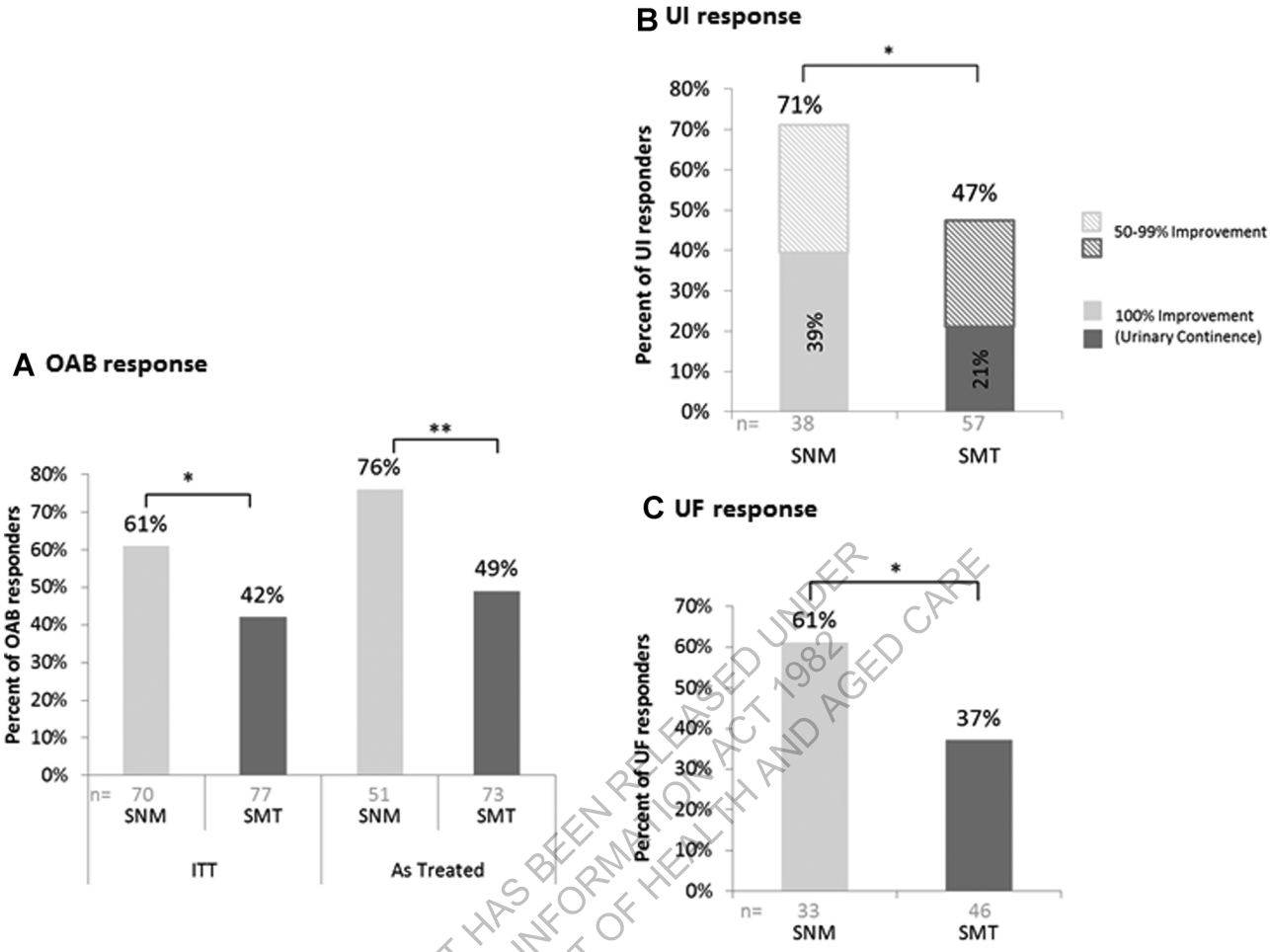

Fig. 2. Overactive bladder therapeutic response. **Panel A**: Intent to Treat (ITT): Includes all randomized subjects (including SNM subjects not implanted). Data for subjects without 6-month diary data were assumed to be treatment failures. As Treated: Includes subjects with diary data at baseline and 6 months (124/147); subjects are grouped based on treatment received: SNM includes all implanted subjects, SMT includes all subjects not implanted. **Panels B** and **C**: UI responder was defined as ≥50% improvement in leaks/day. UF responder was defined as ≥50% improvement in voids/day or a return to normal voiding frequency (<8 voids/day). $^{*}P < 0.05$; $^{**}P < 0.01$.

trial where subjects had a mean of 9.5 leaks[8] and 16.0 voids[7] per day at baseline. These new findings indicate SNM is an effective therapy in refractory subjects with less severe OAB symptoms who experienced inadequate symptom control and/or unacceptable adverse drug events with at least one anticholinergic medication, and does not require failing all medications before offering as a therapeutic option.

In addition to the objective improvements, this study also demonstrated a significant difference in subjective measures, favoring SNM over SMT. All domains of the ICIQ-OABqol showed greater improvement in the SNM group compared to the SMT group (all $P < 0.001$). For the domains of Concern, Coping, Sleep and HRQL, score changes for SNM were greater than 3.5 times the minimally important difference (MID); while in the SMT group, the score changes were 1–1.5 times the MID. In addition there were greater improvements in sexual function for females and depression scores for SNM compared to SMT.

Recent published multicenter trials for other OAB therapies demonstrated a failure to meet their primary efficacy outcome comparison to anticholinergic medication, indicating they were not more efficacious than drug. The Orbit trial randomized 100 subjects to SMT versus percutaneous tibial nerve stimulation (PTNS). While the subjective improvement was greater for PTNS, the objective changes measured were not significantly different.[13] In the ABC trial, subjects were randomized to either anticholinergic therapy versus a single dose of 100 units of intravesical onabotulinum toxin (BoNT) injected at 20 sites.[14] The study demonstrated no significant difference in the primary outcome of number of incontinence episodes, nor secondary outcomes of QOL between the two treatments at 6 months. While there is yet to be a completed trial comparing either PTNS or intravesical BoNT to SNM, these recent studies provide a context for comparison. PTNS and BoNT did not show an objective benefit compared to SMT, while this trial showed SNM to be objectively and subjectively superior to SMT. An additional alternative OAB treatment (mirabegron, a β3 adrenergic agonist) has been recently approved although efficacy has not been evaluated in comparison to SNM or other treatment options.

The rate of device-related AEs observed in the InSite study are improved compared to those reported earlier.[7,8,15,16] Importantly, only a small number of reported AE's in the two groups were serious. Two subjects discontinued due to an AE, but only one of these was device-related (infection of the incisional site and device tract).

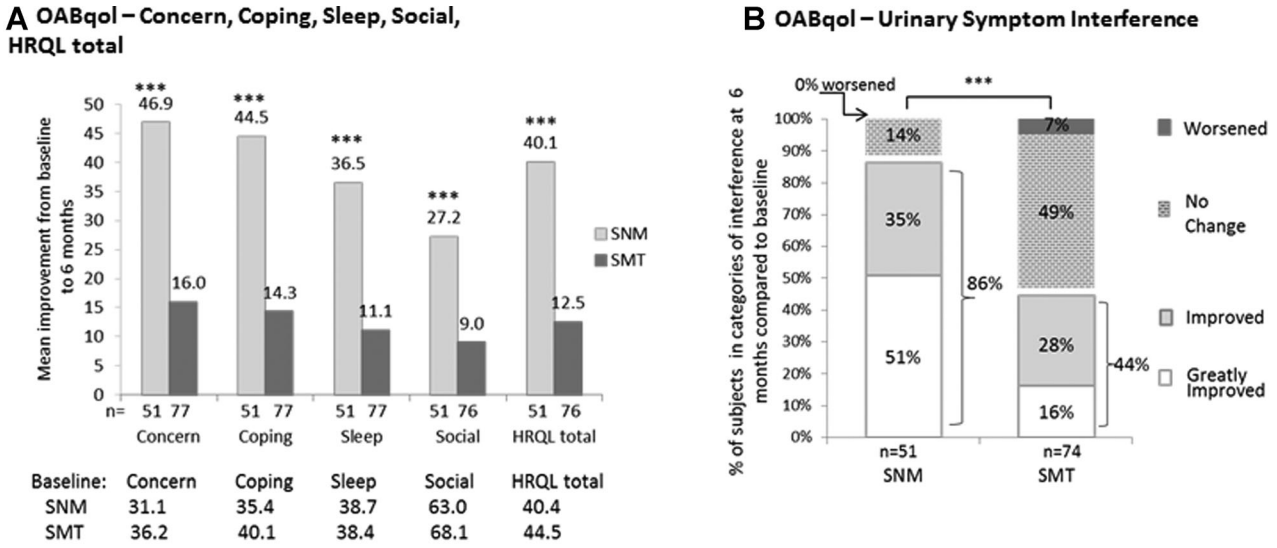

Fig. 3. Results of OAB quality of life comparison between SNM and SMT at 6 months from baseline. As shown in **Panel A**, all measures (Concern, Coping, Sleep, Social, and HRQL total) showed greater improvement at 6 months in the SNM group compared to the SMT group (all $P < 0.001$). MID, minimally important difference. The MID is the smallest score change that is perceived beneficial to patients and is often used to determine whether changes in scores are considered clinically significant.[17] The MID for the OABqol subscales has been suggested to be 10 points.[18] As shown in **Panel B**, there is a significant difference between SNM and SMT in improvement of urinary symptom interference from baseline at 6 months ($P < 0.001$). *** $P < 0.001$; between group comparison.

The primary strength of this study is its prospective, randomized design, which provides level-one evidence of the benefit of SNM over SMT in a population of subjects with relatively milder symptoms of OAB. Additionally, the large number of academic and private practice centers enrolling subjects make the data more generalizable and reflective of outcomes from standard clinical practice. A weakness of the study is the homogenous, predominantly Caucasian subject population, making the results less generalizable to the overall population. Additionally, the lack of blinding of randomized treatment must be acknowledged as a potential weakness. It was deemed very difficult to include in the current study due to the inability to blind patients from sensing stimulation and the ethical considerations of a sham device implantation for an approved therapy as well as the fact that a blinded assessment of the therapy had occurred previously as part of the original device approval trial.

The response to SMT measured in this study was higher than expected. Some possible explanations include the study aim to focus on subjects with less severe symptoms and the use of newer pharmacological options. Subjects with severe symptoms, or who were motivated to receive SNM instead of SMT, were eligible to obtain neuromodulation outside of the protocol as a standard treatment. Additionally, careful monitoring of compliance, improved tolerability of newer agents, and the opportunity to switch medications within SMT may have played a role in the outcomes. Even with the high rate of benefit from SMT measured in this study, there was a 20–30% advantage for SNM.

CONCLUSION

This study demonstrates that SNM provides superior objective and subjective outcomes compared to SMT for symptoms of UI and UF. Additionally, there was an improved AE profile for SNM than previously reported. This subject population was a less severe and refractory group than previously studied, demonstrating that SNM is a successful option for subjects who experienced inadequate symptom control and/or unacceptable adverse drug events with at least one anticholinergic medication throughout the OAB spectrum. This study suggests that after unsuccessful treatment with one or more anticholinergic medications, OAB subjects are more likely to benefit from SNM than an additional anticholinergic as a next step.

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DISEASES OF THE COLON & RECTUM

ORIGINAL CONTRIBUTION

Sacral Nerve Stimulation is more Effective than Optimal Medical Therapy for Severe Fecal Incontinence: A Randomized, Controlled Study

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PURPOSE: This randomized study was designed to compare the effect of sacral neuromodulation with optimal medical therapy in patients with severe fecal incontinence.

METHODS: Patients (aged 39–86 years) with severe fecal incontinence were randomized to have sacral nerve stimulation (SNS group; n=60) or best supportive therapy (control; n=60), which consisted of pelvic floor exercises, bulking agent, and dietary manipulation. Full assessment included endoanal ultrasound, anorectal physiology, two-week bowel diary, and fecal incontinence quality of life index. The follow-up duration was 12 months.

RESULTS: The sacral nerve stimulation group was similar to the control group with regard to gender (F:M=11:1 *vs.* 14:1) and age (mean, 63.9 *vs.* 63 years). The incidence of a defect of ≤ 120° of the external anal sphincter and pudendal neuropathy was similar between the groups. Trial screening improved incontinent episodes by more than 50 percent in 54 patients (90 percent). Full-stage sacral nerve stimulation was performed in 53 of these 54 "successful" patients. There were no septic complications. With sacral nerve stimulation, mean incontinent episodes per week decreased from 9.5 to 3.1 ($P<0.0001$) and mean incontinent days per week from 3.3 to 1 ($P<0.0001$). Perfect continence was accomplished in 25 patients (47.2 percent). In the sacral nerve stimulation group, there was a significant ($P<0.0001$) improvement in fecal incontinence quality of life index in all four domains. By contrast, there was no significant improvement in fecal continence and the fecal incontinence quality of life scores in the control group.

CONCLUSIONS: Sacral neuromodulation significantly improved the outcome in patients with severe fecal incontinence compared with the control group undergoing optimal medical therapy.

KEY WORDS: Sacral nerve stimulation; Fecal incontinence.

Fecal incontinence is debilitating and affects approximately 2 percent of the population.[1] The prevalence increases with age, and after aged 50 years, prevalence rates up to 11 percent in men and 26 percent in women have been reported.[2,3] The standard management for symptomatic fecal incontinence includes nonoperative management, such as use of bulking agents, pelvic floor exercises, dietary changes, or by repair of a localized sphincter defect.[4,5] However, the long-term result of a sphincter repair is unpredictable and often poor.[6] Sphincter replacement with artificial bowel sphincter[7] or graciloplasty[8] is used as salvage therapy for end-stage fecal incontinence, but both options are associated with substantial morbidity.

More recently, sacral nerve stimulation has been advocated as a safe and effective therapy for severe fecal incontinence with minimal morbidity.[9–11] Most reports on sacral nerve stimulation comprise a small number of patients from single centers.[12,13] There has been no randomized trial. The efficacy of sacral nerve stimulation in patients with pudendal neuropathy[13] or sphincter defect[14,15] also is controversial.

This is the only randomized trial that has compared sacral nerve stimulation with optimal medical therapy (bulking agents, dietary management, pelvic floor exercises) in patients with significant fecal incontinence by evaluating their respective efficacy and impact on quality of life.

PATIENTS AND METHODS

From March 2004 to March 2006, a prospective, randomized trial of 120 patients with significant fecal incontinence (Wexner's incontinence score > 12) was performed, comparing sacral nerve stimulation (SNS group) with optimal

[a]Deceased.

Read at the meeting of The American Society of Colon and Rectal Surgeons, St. Louis, Missouri, June 2 to 6, 2007.

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medical therapy (control group). All patients attended a multidisciplinary pelvic floor clinic. Randomization was performed from the central registry by using sealed envelopes. Optimal medical therapy comprised bulking agents, pelvic floor exercises with a team of dedicated physiotherapists, and dietary management on fluid and fibers with a team of dieticians. The frequency of attendance of control patients with a pelvic floor team varied between patients, depending on needs; generally this was at monthly intervals for the first six months and two-monthly intervals for the second six months. Each pelvic floor exercise session lasted 20 minutes. Biofeedback was provided with digital guidance. Patients were asked to perform identical sets of 50 contractions twice per day at home. Both the SNS and control groups were seen by the primary investigators for formal assessment at baseline, 3 months, 6 months, and 12 months after recruitment. Inclusion criteria for the randomized trial included: involuntary passage of solid or liquid stool at least once per week, refractory to medical therapy and pelvic floor exercises, and aged 35 to 86 years. Exclusion criteria included: rectal prolapse, inflammatory bowel disease, congenital anorectal malformation, neurologic disorders such as Parkinson's disease, multiple sclerosis, spinal-cord injury, stoma *in situ*, pregnancy, external anal sphincter defect of more than 120° of the circumference, bleeding diathesis, and mental or physical disability precluding adherence to study protocol. Defects of the internal anal sphincter alone did not preclude inclusion in the study. Ethics approval was obtained from the institution review board of the participating hospitals, and every patient provided written, informed consent.

Baseline assessment included physical examination, rigid sigmoidoscopy, anorectal manometry, pudendal nerve terminal motor latency (PNTML) measurement,[16] endoanal ultrasound,[5] Wexner's incontinence score,[17] fecal incontinence quality of life index (FIQL),[18] the standard short form-12 (SF-12) health survey questionnaire,[19] and a two-week bowel diary. The FIQL was used to measure four domains (lifestyle, coping/behavior, depression/self-perception, and embarrassment) of quality of life in association with fecal incontinence.[18] The SF-12 is not disease-specific and measures quality of life in the domains of physical health (PH) and mental health (MH); a higher score indicated a better function.[19] Anorectal manometry was performed by using a pull-through technique with an eight-channel water-perfused system previously described.[16] Measurements were made by using the standard nomenclature adopted by the International Working Party.[20] A PNTML longer than 2.6 ms (beyond 2 standard deviations in our laboratory) was defined as having pudendal neuropathy.[21] Incontinent episodes were classified as urge (inability to defer defecation) or passive (no awareness of loss of stool). All patients in the study had both urge and passive fecal incontinence.

Follow-up assessment during subchronic test stimulation and 3, 6, and 12 months after implantation included daily bowel diaries for 2 weeks, fecal incontinence quality of life index (FIQL) of The American Society of Colon and Rectal Surgeons, and the standard short form-12 health survey quality of life questionnaire (SF-12). During the assessment period, antidiarrheal medications were avoided in all patients in the SNS group. In the medical therapy group (control), Imodium® (Janssen-Cilag, Titusville, NJ) was used in 11 patients as a bulking agent to help improve continence; 6 of these patients for less than four months, and the remainder for between four to seven months. For the remaining patients in the control group, antidiarrheal medications were similarly avoided during the study period.

The follow-up duration was for 12 months, and all adverse events were noted. There was complete compliance with follow-up in both groups of patients.

Procedures

All procedures were performed by a single operator (JJT), in a standard fashion, as previously described.[9] General anesthesia was administered without neuromuscular junction nerve blockade. All patients underwent a diagnostic screening phase with peripheral nerve evaluation.[9] Intraoperatively, a 20-gauge, 3.5-inch, insulated foramen electrode was inserted bilaterally into the third sacral foramina (S3) and was then stimulated by using an external pulse generator (Medtronic Interstim™ model 3625, Minneapolis, MN). The optimal foramen which elicits the best motor (*i.e.*, "bellows" contraction of the perineum and contraction of the ipsilateral great toe) with the least voltage was selected for subchronic stimulation. Subchronic stimulation was performed with a percutaneously placed test stimulation lead (Medtronic Interstim™ model 3057) attached to an external pulse generator (Medtronic Interstim™ model 3625).

All patients were tested for a minimum of seven (mean 10.1, SD 2.1) days. Patients who have had a good response during the screening period, as defined by 50 percent or greater reduction in incontinent episodes per week or 50 percent or greater reduction in the number of days with incontinence per week based on the two-week bowel diary, underwent permanent implantation with a quadripolar electrode (Medtronic Interstim™ model 3080) and the pulse generator (Medtronic Interstim™ model 3023), which was placed subcutaneously in the gluteal area.

The pulse generator was activated by telemetry the morning after surgery. The electrode combination that gave the patient the best perception of muscle contraction of the perineum and anal sphincters with the least voltage was chosen for permanent stimulation. Stimulation was cycling (20 seconds on and 8 seconds off) with a pulse width of 210 microseconds, a frequency of 19 pulses per second, and current amplitude adjusted to the patient's perception of muscular contraction.

Statistical Analysis

Data were provided as mean and standard deviation. Statistical analysis was performed by using two-tailed, Wilcoxon's signed-rank test or Mann-Whitney *U* test to compare patient data between groups. Fisher's exact test was used to compare categorical data. $P<0.05$ was considered statistically significant; however, adjustments were made to determine significance level by allowing for multiple comparisons. Thus, statistical significance was reached for Wexner's continence score if $P<0.01$; for SF-12 and anorectal manometry, if $P<0.025$ (0.05/2), and for the four FIQL components, $P<0.0125$ (0.05/4) was significant. Kruskal-Wallis test was used to assess the relationship between the presence of unilateral or bilateral pudendal neuropathy and the improvement in outcome parameters. All statistical analysis was performed with SPSS® software (version 13.0; SPSS Inc., Chicago, IL).

RESULTS

A total of 120 patients were randomized to undergo treatment with sacral nerve stimulation (SNS group) or optimal medical therapy (control group) with bulking agents, pelvic floor exercises, and dietary management. Patients' demographics and characteristics were similar between the two groups (Table 1). Incontinence scores and quality of life parameters (Wexner's incontinence score, FIQL, SF-12) also were comparable between groups (Table 1).

In the control group undergoing optimal medical therapy, there was no significant improvement in fecal continence as assessed by the two-week bowel diary or Wexner's score, FIQL scores and SF-12 quality of life scale. (Table 2) There were no significant changes in the maximum resting and squeeze anal canal pressures.

Of the SNS group, successful cannulation of foramen electrode was achieved in all but one patient who had

Table 1. Patient demographics

	Sacral Nerve Stimulation		*Control group*	*P value (PNE vs. Control group)*
	PNE	*Complete SNS*		
	(n=60)	*(n=53)*	*(n=60)*	
Age (yr)	63.9±13.2	63.4±12.9	63±12.1	NS
Gender (female:male)	11:1	12.3:1	14:1	NS
Prior sphincter repair	31 (52)	29 (55)	35 (58)	NS
Prior anterior resection	3 (5)	3 (6)	3 (5)	NS
Prior anorectal surgery				
Hemorrhoidectomy	11 (18)	10 (19)	13 (22)	NS
Sphincterotomy	3 (5)	3 (6)	5 (8)	NS
Spinal cord injury (lumbar)	1 (1.6)	1 (1.9)	1 (1.6)	NS
External anal sphincter				
Intact	30 (50)	28 (53)	32 (53)	NS
Defect/scar	30 (50)	25 (47)	28 (47)	NS
Anorectal physiology				
Anal pressure (mmHg)				
Resting	30.4±13	29.7±11.7	31.2±11.2	NS
Squeeze	63.5±33.1	61.2±29.1	65.1±31.3	NS
PNTML > 2.6 ms	39 (65)	36 (68)	41 (68)	NS
Unilateral	20 (33)	19 (36)	19 (32)	NS
Bilateral	19 (32)	17 (32)	22 (37)	NS
Wexner's score	16.0±1.3	16.0±1.3	15.2±1.6	<0.05
Bowel diary				
Number of incontinent episodes/week	9.9±12.8	9.5±12.8	9.2±13.4	NS
Days with incontinence/week	3.3±2.4	3.3±2.4	3.3±2.1	NS
Days with staining/week	4±2.3	4±2.3	4.3±1.9	NS
Days with pads per week	3.8±3	3.8±3	3.7±3.4	NS
Fecal incontinence quality of life (FIQL) index				
Lifestyle	2.36±0.97	2.39±0.99	2.26±0.98	NS
Coping / behavior	1.9±0.79	1.89±0.82	1.79±0.82	NS
Depression / self-perception	2.62±0.81	2.65±0.84	2.59±0 .72	NS
Embarrassment	1.92±0.75	1.93±0.78	1.81±0.52	NS
Short form-12 (SF-12) quality of life scale				
Physical health	39.4±11.42	39.81±11.14	39.29±12.12	NS
Mental health	44.3±11.56	45.25±11.09	45.38±12.32	NS

PNE=peripheral nerve evaluation; SNS=sacral nerve stimulation; PNTML=pudendal nerve terminal motor latency; NS = not significant. • Data are means±standard deviations or number of patients with percentages in parentheses.

Table 2. Analysis of bowel diary and Wexner's score in the control group

	Baseline	*3 months**	*12 months**
Wexner's score	15.2±1.6	12.1±2.1	14.1±1.9
Bowel diary			
Number of incontinent episodes/week	9.2±13.4	8.1±14.1	9.4±11.8
Days with incontinence/week	3.3±2.1	2.9±2.4	3.1±1.8
Days with staining/week	4.3±1.9	4.5±2.1	4.5±2.3
Days with pads per week	3.7±3.4	3±3.8	3.2±3.1
Fecal incontinence quality of life (FIQL) index			
Lifestyle	2.26±0.98	2.12±0.91	2.31±0.89
Coping / behavior	1.79±0.82	1.85 ± 0.92	1.86 ± 0.88
Depression / self-perception	2.59±0 .72	2.68 ± 0.65	2.64 ± 0.84
Embarrassment	1.81±0.52	1.7±0.67	1.78±0.61
Short form-12 (SF-12) quality of life scale			
Physical health	39.29±12.12	41.5±9.89	40.5±10.2
Mental health	45.38±12.32	47.82±10.66	48.22±10.12

Data are means±standard deviations. • *The P value for each outcome at 3-month and 12-month compared with baseline was > 0.05.

previous back surgery, requiring the use of bone graft from the sacral area. Of the remaining 59 patients, 54 had 50 percent or greater improvement in continence during subchronic test stimulation; 1 of these 54 patients elected not to proceed to a permanent implant because of concerns that she might require magnetic resonance imaging of her brain after excision of a meningioma eight years previously. In total, 53 patients in the SNS group underwent a permanent sacral nerve implant, positioned through the third sacral nerve foramina. Initial mean amplitude of stimulation of the permanent sacral nerve implant was 1.27 V (SD, 0.82). During 12-month follow-up, the program needed readjustment for a mean of 3 occasions (SD, 0.25) in all patients, largely to maintain efficacy and patient perception of stimulation. Adjustment of the program has included combinations of changes in the electrode used for stimulation, amplitude and rate. At 12-month follow-up, mean amplitude was 2.12 V (SD, 1.28).

Fecal continence was greatly improved with chronic sacral nerve stimulation immediately after implantation and was sustained during the follow-up period. Incontinent episodes per week improved from a mean of 9.5 (SD, 12.8) at baseline to 4.2 (SD, 12.3; $P<0.0001$) at 6 months and to 3.1 (SD, 10.1; $P<0.0001$) at 12 months. Both urge and passive incontinence improved substantially. Table 3 and Figure 1 show that there was a significant decrease in the number of incontinent episodes per week, the number of incontinent days per week, fecal staining, and use of pads. Ability to defer defecation also improved significantly (Fig. 2A). However, ability to completely empty the bowel was not affected (Fig. 2B).

Table 3. Analysis of Wexner's score, anorectal manometry, and bowel diary in the SNS group

	Baseline	*Screening with PNE*	*3 months*	*6 months*	*12 months*
Wexner's score*	16±1.3	1.2±0.9	1.1±1	Not reported	1.2±1.8
Anorectal Manometry					
Resting pressure†	29.7±11.7	32±11.2	32.8±16.9	30±16.9	30.1±16.1
Squeeze pressure†	61.2±29.1	50.2±15.9	63.4±32.6	66.1±39	66.3±40.4
Bowel diary					
Incontinent episodes/week*	9.5±12.8	0.7±1.6	2.9±6.3	4.2±12.3	3.1±10.1
Days with incontinence/week*	3.3±2.4	0.3±0.5	1±1.7	1.1±1.8	1±1.7
Days with staining/week*	4±2.3	0.6±1.1	1.3±1.7	1.6±2.1	1.4±2
Days using pads/week*	3.8±3	1.1±2.2	1.6±2.6	1.6±2.6	2.2±3
Fecal incontinence quality of life (FIQL) index					
Lifestyle‡	2.39±0.99	2.79±0.95[¡]	3.34±0.72	3.24±0.79	3.31±0.72
Coping / behavior‡	1.89 ± 0.82	2.33±0.97[¶]	2.87±0.8	2.71±0.82	2.68±0.87
Depression / self perception‡	2.65±0.84	2.94±0.88[#]	3.31±0.77	3.31±0.79	3.25±0.8
Embarrassment‡	1.93±0.78	2.36±1**	2.89±0.85	2.83±0.87	2.76±0.94
Short form-12 (SF-12) Quality of life scale					
Physical health§	39.81±11.14	41.66±9.13	43.18±11.68	42.49±11.16	42.22±9.25
Mental health§	45.25±11.09	47.32±10.45	50.16±10.41	49.22±10.13	49.22±10.88

SNS=sacral nerve stimulation; PNE=peripheral nerve evaluation. • Data are means±standard deviations. • *$P<0.0001$ when comparing outcomes at all time-points with baseline. • †$P>0.05$ when comparing outcomes at all time-points with baseline. • ‡$P<0.0001$ when comparing outcomes at 3-months, 6-months, and 12-months with baseline. • §$P>0.025$ at all time-points except for mental health at three-months ($P=0.005$) and six-months ($P=0.005$). • ¡$P=0.014$; ¶$P=0.002$; #$P=0.031$; **$P=0.016$.

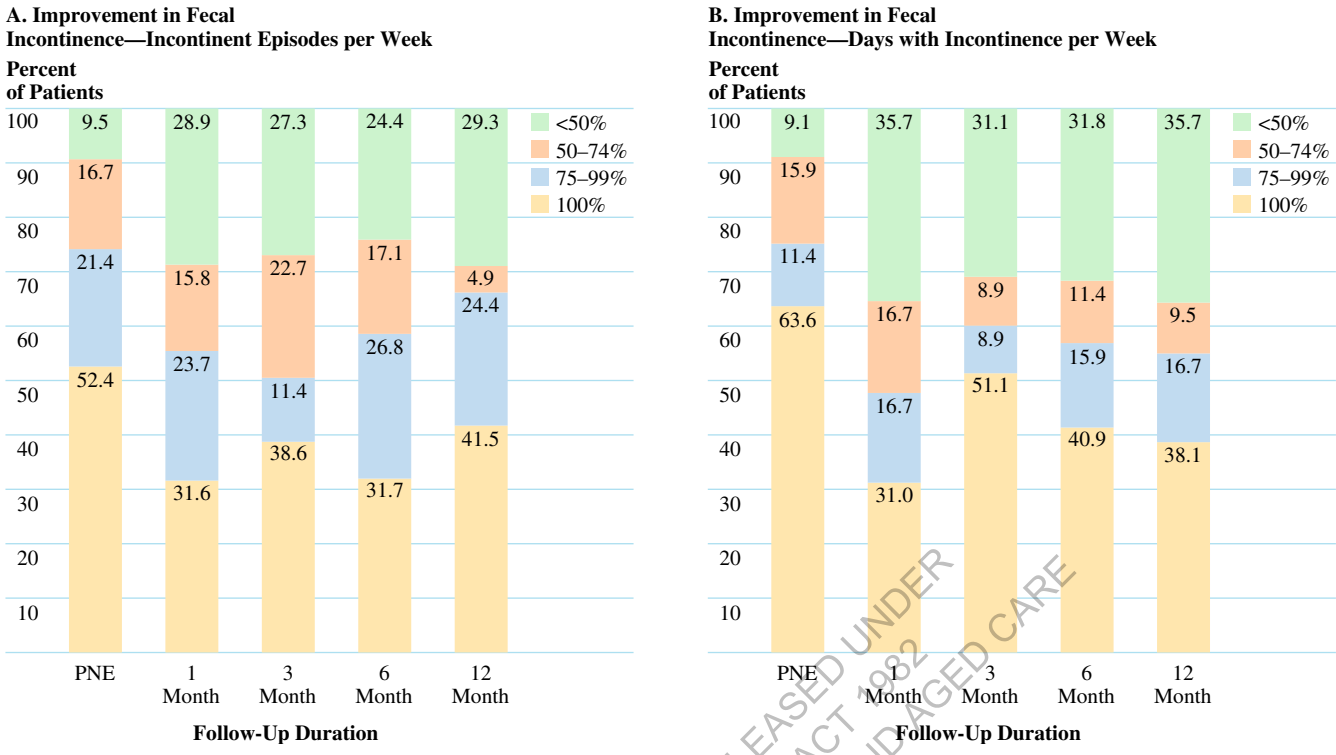
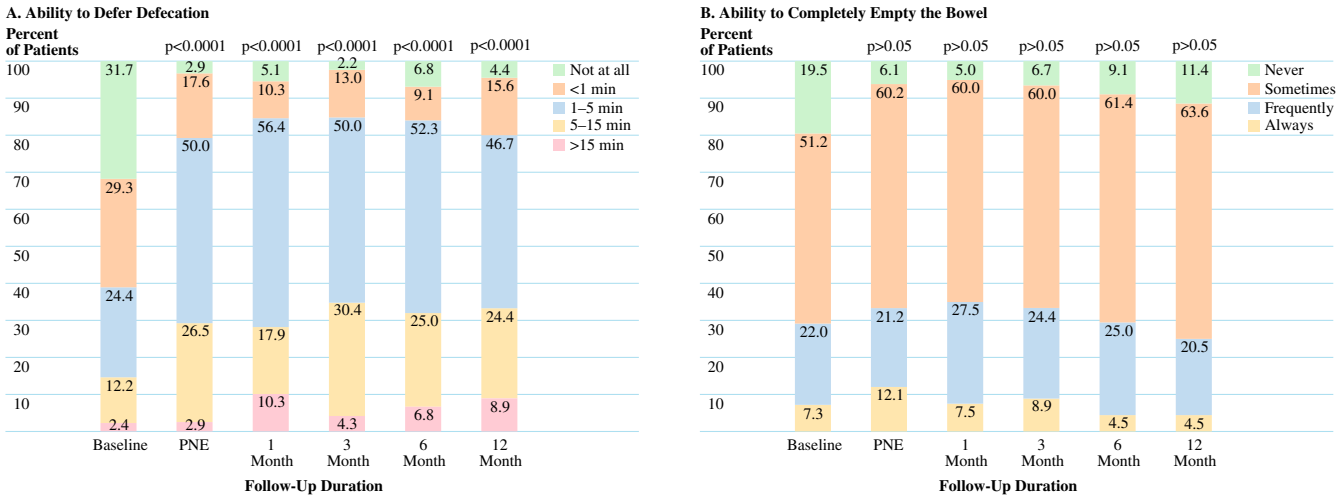


FIGURE 1. Improvement in fecal incontinent episodes per week (A) and in days with fecal incontinence per week (B) during sacral nerve stimulation. PNE = peripheral nerve evaluation.

Perfect continence was accomplished in 25 patients (47.2 percent). Twenty-two patients (41.5 percent) and 13 patients (24.4 percent) had 100 percent and 75 to 99 percent improvement, respectively, in incontinent episodes per week. None of the patients have had worsening of fecal continence as a result of sacral nerve stimulation. All three patients who have had ultralow (n=2) or low (n=1) anterior resection of rectum have had significant improvement, with improvement in incontinent episodes per week of 100 percent (n=1), 75 to 99 percent (n=1), and 50 to 74 percent, respectively. A single patient with lumbar spinal injury also has a significant improvement of 50 to 74 percent in both the incontinent episodes and incontinent days per week with sacral nerve stimulation.

FIGURE 2. Ability to defer defecation (A) and to completely empty the bowel (B) during sacral nerve stimulation. PNE = peripheral nerve evaluation.



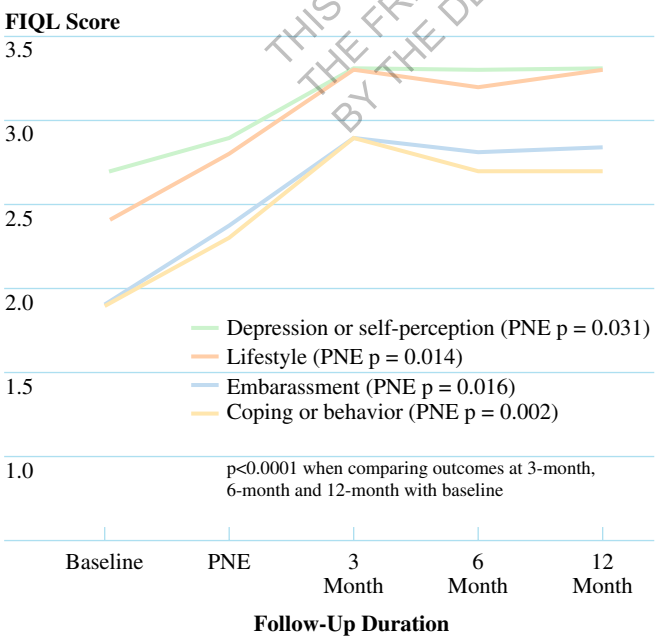
There was a significant improvement in all four scales of FIQL, evident immediately after implantation (Table 3; Fig. 3). There was no significant improvement in both the physical and mental health scale of SF-12 throughout the follow-up period, except in the mental health scale at three months (P=0.005) and six months (P=0.005) after full-stage sacral nerve implant (Fig. 4).

Neither the maximum resting nor squeeze anal canal pressures changed significantly during the screening trial with peripheral nerve evaluation at 3, 6, and 12 months of chronic sacral nerve stimulation. Baseline pudendal nerve terminal motor latency has no association with the improvement, at 12-month follow-up, in incontinent episodes per week (P=0.66) or incontinent days per week (P=0.59) related to sacral nerve stimulation.

Adverse events with SNS included pain at implant site especially in slimmer patients (6 percent), seroma (2 percent), which resolved after percutaneous aspiration, and excessive tingling in the vaginal region (9 percent). There was no septic complication requiring explantation. There was no adverse event associated with urinary or sexual function. In the control group, six patients complained of constipation as the result of treatment with Imodium®.

The SNS group has significantly better functional outcome than the control group in terms of fecal continence and FIQL scores throughout the entire study (Table 4).

FIGURE 3. Fecal incontinence quality of life assessment (FIQL score) in the sacral nerve stimulation group. SNS = sacral nerve stimulation; FIQL = Fecal incontinence quality of life scale; PNE = peripheral nerve evaluation.



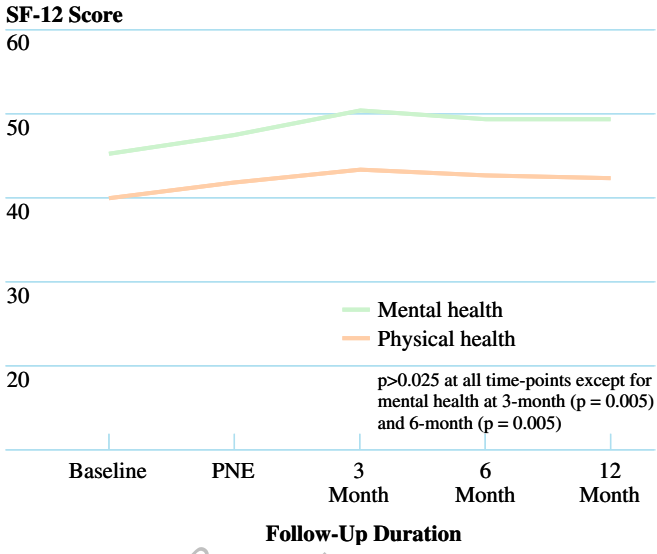


FIGURE 4. SF-12 quality of life assessment in the sacral nerve stimulation group. SNS = sacral nerve stimulation; SF-12 = short form-12 health survey; PNE = peripheral nerve evaluation.

DISCUSSION

This study has shown clearly that at 12-month follow-up sacral nerve stimulation is much more effective than supervised optimal medical therapy that comprises bulking agents, pelvic floor exercises, and dietary management. The presence of a control group has helped to reject the concept of a placebo effect of sacral nerve stimulation-an observation that has been suggested in a previous cross-over study.[22] More than half the patients have had a previous sphincter repair and approximately two-thirds of patients had evidence of pudendal neuropathy. Close to half the patients in the SNS group had evidence of a defect (120° or less) of external anal sphincter. Despite presence of such a significant pathophysiology, the results of sacral nerve stimulation have been impressive, with 41.5 percent and 24.4 percent of patients, respectively, having had 100 percent and 75 to 99 percent improvement in incontinent episodes per week. In addition, perfect continence was achieved in 47.2 percent of patients. In particular, none of the patients has deterioration of fecal continence after chronic sacral nerve stimulation. Sacral nerve stimulation seems to be effective in treating fecal incontinence associated with a wide range of contributing factors (Table 1). The efficacy of SNS in treating fecal incontinence following a low or ultralow anterior resection in this study might provide an expanded indication for its use.

In addition to a sustained functional improvement, quality of life was significantly enhanced as measured by fecal incontinence quality of life (FIQL) scores; this is to

Table 4. Comparison of outcomes between the SNS and the control group

	3-month			12-month		
	SNS group	*Control group*	*P value*	*SNS group*	*Control group*	*P value*
Wexner's score	1.1±1	12.1±2.1	0.0001	1.2±1.8	14.1±1.9	0.0001
Bowel diary						
Incontinent episodes/week	2.9±6.3	8.1±14.1	0.0149	3.1±10.1	9.4±11.8	0.0031
Days with incontinence/week	1±1.7	2.9±2.4	0.0001	1±1.7	3.1±1.8	0.0001
Days with staining/week	1.3±1.7	4.5±2.1	0.0001	1.4±2	4.5±2.3	0.0001
Days using pads/week	1.6±2.6	3±3.8	0.0261	2.2±3	3.2±3.1	0.0851
Fecal incontinence quality of life (FIQL) index						
Lifestyle	3.34±0.72	2.12±0.91	0.0001	3.31±0.72	2.31±0.89	0.0001
Coping/behavior	2.87±0.8	1.85±0.92	0.0001	2.68±0.87	1.86±0.88	0.0001
Depression / self perception	3.31±0.77	2.68±0.65	0.0001	3.25±0.8	2.64±0.84	0.0001
Embarrassment	2.89±0.85	1.7±0.67	0.0001	2.76±0.94	1.78±0.61	0.0001
Short form-12 (SF-12) quality of life scale						
Physical health	43.18±11.68	41.5±9.89	0.4095	42.22±9.25	40.5±10.2	0.3522
Mental health	50.16±10.41	47.82±10.66	0.2416	49.22±10.88	48.22±10.12	0.6138

SNS=sacral nerve stimulation. • Data are means ± standard deviations unless otherwise indicated.

be expected because fecal incontinence is socially disabling.[23] Changes in SF-12 quality of life scores in both the physical and mental life scales were not as significant as FIQL in this study. This is somewhat surprising; however, SF-12 is an assessment for general well-being and is affected by many factors that might interfere with the benefits from an improved fecal continence. A similar observation was noted in another study on injectable silicone biomaterial from our center.[24]

Screening trial with peripheral nerve evaluation is the single most important predictive test for response to SNS; all patients in this study who have had a good response to the screening trial had a good and sustained response to permanent implant. Thus, screening trial with peripheral nerve evaluation is essential in selecting appropriate patients for SNS. Migration of the temporary test stimulation lead during screening trial has not been a problem in this study, largely because of the secure manners the electrode was taped in place. Compared with permanent quadripolar lead, test stimulation lead is relatively inexpensive, fully reversible, and easy to remove in the office without the need for any anesthesia, which is required for removal of a quadripolar lead. In addition, temporary test stimulation lead also provides the flexibility, in selected cases, insertion of a lead on each side (right and left S3) to ascertain the side with the best clinical response; this would have been impractical with the much more expensive quadripolar lead.

In this study, 29.3 percent of SNS patients have an improvement in incontinent episodes per week of less than 50 percent. A recent study has similarly shown that there is an unexplained secondary loss of therapeutic effect in approximately one-third of patients, especially of nonneurologic fecal incontinence, treated by permanent sacral nerve stimulation.[13] There is no other clear predictor of success for chronic sacral nerve stimulation. The presence of pudendal neuropathy did not have an impact on the outcome of SNS in our study, although this is an area of controversy because some authors[9] believe that an intact pudendal nerve function and a normal nerve-muscle connection are essential for a good outcome with sacral nerve stimulation . Increasingly it is accepted that pudendal nerve terminal motor latency has a limited predictive value.[9,10] A recent report has suggested that fecal incontinence of neurologic origins is more likely to have a good outcome from SNS.[13] We have included patients with moderate defect of external anal sphincter, up to 120° of the circumference. A recent report has supported this observation in noting that patients with a sphincter defect of less than 33 percent of the circumference had equivalent results as those having intact sphincters.[25]

The average patient needs adjustment of the sacral nerve program on three occasions in the first 12 months. This is likely that inward migration or changes of the position of the electrode to the sacral nerve (S3) occurs in the early postoperative period. With time, adhesions and fibrosis are likely to stabilize the position of the electrode. Thus, it is important that patients are regularly followed-up after implantation of SNS, and physicians ought to be familiar with sacral nerve programming.

The efficacy of SNS is unlikely to mediate significantly through the sphincter mechanism, because there was no significant increase in both the maximum resting and squeeze anal canal pressures in this or other studies.[9,26,27] Some investigators, however, have shown increases in resting and/or squeeze anal canal pressures,[15,28,29] and there was a general belief that the improved continence in SNS was attributed to a direct stimulation on the external anal sphincter.[9] Other hypotheses on the mechanism of action of SNS have included effect on autonomic nervous system,[15,28] modulation of anorectal reflexes,[12] modulation of corticospinal pathway,[30] and changes in rectal sensitivity and

motility.[16,31,32] The precise mechanism of action of sacral nerve stimulation remains speculative at this stage.

The procedure seems to be safe, with minimal complications. In particular, with meticulous aseptic techniques there were no septic complications. This could be partly attributed to the fact that none of the patients had a permanent quadripolar lead (Medtronic Interstim™ model 3080) during the screening phase. The use of a permanent quadripolar lead for screening trial might be associated with a higher septic complication.[9,33] When choosing an appropriate therapy for patients with end-stage fecal incontinence, the safety profile of SNS compared with the higher complication rates of other alternative procedures, such as dynamic graciloplasty or artificial bowel sphincter, should be taken into account. [6]

Our study is somewhat limited because the follow-up was only for 12 months. However, some of our control patients who underwent optimal medical therapy have found it difficult to continue with their disability and have sought therapy with SNS after the 12-month study. Longer follow-up of all our SNS patients is in progress and shall be separately reported. The lack of a dramatic response with medical therapy was surprising, but this could relate to inclusion of patients with more severe fecal incontinence with a high proportion of patients having pudendal neuropathy. For example, in a recent study on biofeedback therapy, only patients with mild-to-moderate fecal incontinence were included.[34]

The safety profile, efficacy, and simplicity of sacral nerve stimulation, even in patients with a limited defect of external sphincter and pudendal neuropathy, would raise consideration of using this therapy as the first-line or second-line surgical therapy, rather than limiting its use for end-stage fecal incontinence. Currently there is an ongoing, randomized trial in our center that compares sacral nerve stimulation with a sphincter repair. Clearly the cost of the device is a concern, but a recent outcome and cost analysis of SNS for fecal incontinence has shown that it is highly cost effective.[35]

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ORIGINAL ARTICLE

Remotely programmed sacral neuromodulation for the treatment of patients with refractory overactive bladder: a prospective randomized controlled trial evaluating the safety and efficacy of a novel sacral neuromodulation device

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Abstract

Purpose The efficacy and safety of a novel remotely programmed BetterStim sacral neuromodulation (SNM) system was evaluated in patients with refractory overactive bladder (OAB) in a prospective, controlled, multicenter trial.

Methods A total of 84 patients referred for SNM therapy from October 2015 to January 2018 were studied. Of the patients who qualified for implantation, 37 and 33 were randomly assigned to treatment and control groups, respectively. Patients in the treatment group underwent stimulation upon implantation, while stimulation was delayed in the control group for 3 months. Follow-up visits, consisting of voiding diary outcome, questionnaires regarding overactive bladder symptom score (OABSS) and quality of life were conducted at 1, 3, and 6-month post-implantation.

Results Compared with the control group, subjects in the treatment group exhibited statistically significant improvement in OAB symptoms at 3 months. The overall success rate was achieved in 72% of the treatment group, compared with 12% of the control group at 3 months. At 6 months, there were no significant differences in key voiding diary variables between the two groups. Further, this study demonstrated sustained improvement in urinary symptom interference in OAB patients. In addition, nearly all patients expressed great satisfaction with the remote-programming methods. No serious adverse events occurred, and device-related adverse events rate was 12.86%.

Conclusion This clinical study demonstrates subjective and objective success of the BetterStim SNM system. Importantly, our data suggest that remote programming can be safely used as a viable option for the conventional programming with a high degree of patient satisfaction.

Keywords Electric stimulation · Urinary bladder · Randomized controlled trial · Overactive bladder · Programming

Introduction

Overactive bladder is a common and chronic clinical syndrome, defined as urinary urgency with or without frequency, typically accompanied with incontinence and nocturia, which becoming a growing problem worldwide [1]. The prevalence is estimated at approximately 16.9% in the adult population and increases with age in the United States [2–4]. The total prevalence of OAB is approximately 6.0% in China [5]. Despite the considerable limitation of social activities and impact of OAB on quality of life, patients rarely seek therapeutic options. For management of refractory overactive bladder, the widely applied sacral neuromodulation therapy may serve as a promising treatment option, with compelling efficacy for OAB symptoms [6–10]. Over the past decades, SNM therapy has gained global acceptance in urological practice and > 250,000 patients have been treated worldwide.

The technique has evolved since its inception by Schmidt et al., with the use of tined lead, as well as the development

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of rechargeable SNM system [11, 12]. However, the SNM system available and approved for use in voiding dysfunctions remains as non-remote programming [6, 13]. Patients require frequently follow-up postoperative programming, and need to come back to hospitals for ensuring the implanted devices are working at optimal programmable parameters and troubleshooting of the implanted devices in vivo. With the popularity of telemedicine, remote point-to-care programming of neuromodulation devices would benefit more patients who live far away from local hospitals.

Currently, a novel BetterStim SNM system (PINS, Beijing, China), manufactured by Beijing PINS Medical Co., Ltd., in cooperation with the National Engineering Laboratory for Neuromodulation, Tsinghua University, is designed to provide a miniaturized, real-time remote-programming system, adjusting the programming parameters timely as tissue impendence changes over time, resulting in continuous and stable clinical benefits. The BetterStim SNM (PINS, Beijing, China) device utilized in the present study includes two series of implantable pulse generator (IPGs): G131 and G132, while the basic components are similar with other SNM systems [6, 12]. The BetterStim IPGs utilize titanium construction and have a volume of 25 cc (dimensions: $47 \times 51 \times 10.5$ mm^3, weight: 35 g) for G131 model and 15 cc (dimensions: $50 \times 50 \times 6.8$ mm^3, weight: 25 g) for G132 model, which is comparative with the 14 cc Medtronic InterStim II. And the battery capacity of G131 and G132 is 2500 mAh and 1850 mAh, respectively, while the InterStim II has a capacity of 1300 mAh, equating to a 30% smaller battery life. Additionally, the BetterStim system could be current controlled or voltage driven, and delivers constant current or voltage stimulation for SNM therapy. As for the BetterStim tined lead, four similarly sized and spaced electrodes to the InterStim lead, measure with three lengths 28, 33 and 41 for different sized patients. One of the most notable differences of the BetterStim system is the significant function of remote controlling, which was refined and well described previously [14]. The remote-programming system is a secure and robust Internet-based system, involving in the application of a virtual network combined with point-to-point encryption software that met recognized standards. Figure 1 shows the general architecture of the real-time remote-programming system: Physician Client, Patient Client, Server Station and Video Communication System. The Physician Client was designed to be located at a personal computer (PC) as the terminal hardware, with strong operability and mobility. Physician could visit the Server Station through a web browser and get detailed information of their patients as well as stimulators. Patient Client was designed as a home terminal for adjusting parameters and uploading follow-up history records. The entire

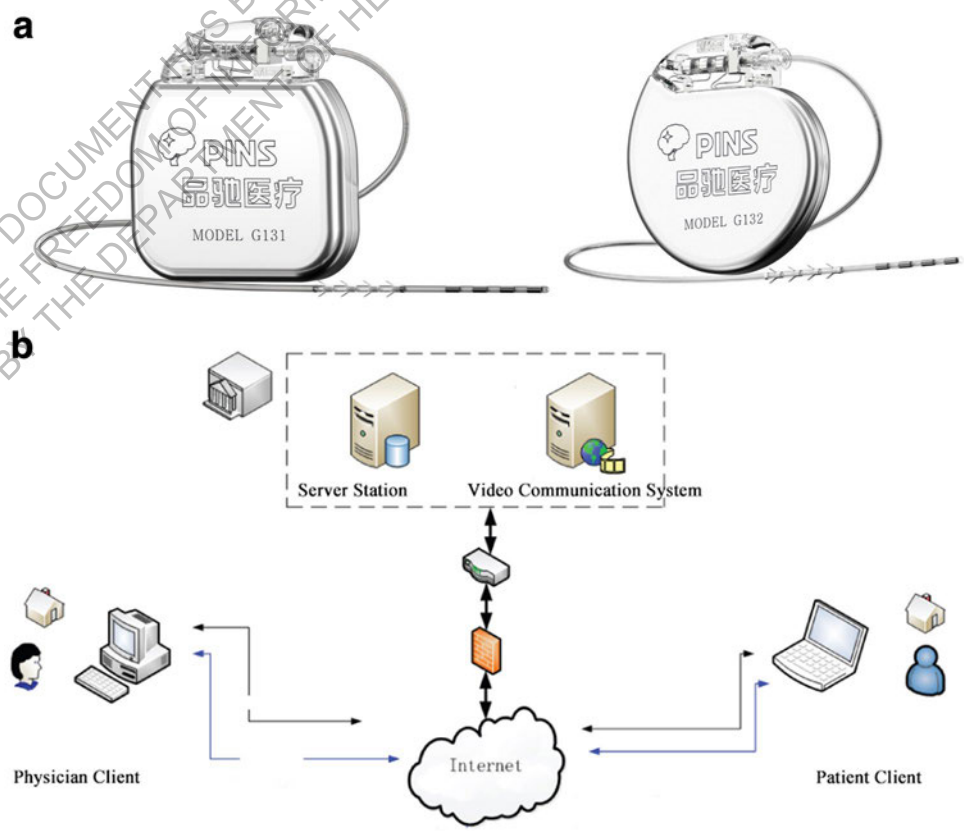

Fig. 1 The remote sacral neuromodulation (SNM) implantable pulse generator system. **a** The SNM implantable pulse generator. **b** Schematic diagram of the wireless and remote-programming system, including the physician client, patient client, server station and video communication system

Patient Client hardware consists of four parts: PC, Bluetooth dongle, programmer and in vivo IPG. The PC is a commercial telephone equipped with a special patient client software downloaded from App store, applying for connecting with the physicians and received programming parameters. The Bluetooth dongle is a custom-built hardware interface and connects to the PC via a USB interface. The programmer installed with a Bluetooth salve unit to exchange data with the Bluetooth dongle and control the in vivo stimulators. The Server Station is established duplex communication channels in which session messages and adjustment parameters are transmitted to the clients and data are stored on the database server. The Video Communication System consists of a live face-to-face electronic audiovisual interaction between the provider and patients. Video was captured by Portable digital USB cameras and microphones. Video (FLV format) and audio (SPEEX format) would be automatically attached into the media stream. The Physician and Patient Client were virtually linked by the Server Station. Via this communication link, the instruction of parameter adjustment was stored and sent to the Patient Client, then transmitted through a wireless link to a patient programmer. Once the implanted stimulator received the instruction from patient programmer and finished the execution, the Patient Client uploaded results and follow-up history records to the Sever Station. SSL protocol and certificate identity authentication were used to establish communication link between the Patient Client and the Server station. The entire remote-programming progress was accompanied by synchronistical visual communication provided by the Video Communication System.

Compared with conventional programming methods, the BetterStim system has significant advantages within all stages of programming, which would reduce costs and travel time for patients, improving patient satisfaction, and facilitate quality care for complex patients [15]. Further, the platform provides real-time remote control service which allows clinicians to directly check the parameters' history records. Some practices such as Bomin Sun use point-to-care programming technology in lieu of conventional programming to see the postoperative Deep Brain Stimulation (DBS) patients, which showed no significant difference in the accuracy of clinical outcomes of programming between the conventional and remote-programming sessions [16, 17]. Additionally, programming parameters of the BetterStim system including amplitude (0–10 V or 0–25 mA), pulse width (30–450 μs), and frequency (2–40 Hz) can be adjusted either by conventional programming or by remote-programming method. To ensure the security of the data transmission, the Physician Client was equipped with a client certificate as an identity authentication which would be examined by the Server Station before the browser gets data. Thus, remote programming can safely use as well as routine postoperative clinic visits in programming.

To confirm the efficacy and safety of this novel remote-programming SNM device (PINS, Beijing, China), we conducted a prospective, multi-center, randomized, control clinical trial in China. The study consisted of an effective analysis that compared OAB clinical therapeutic success in a subset of patients randomized to SNM stimulation ON group or SNM stimulation OFF group and were then followed for 6 months. The primary hypothesis of this randomized procedure was that SNM stimulation would significantly improve OAB symptoms of patients by at least 30% of success rate, superior to SNM OFF group.

Materials and methods

Study design and population

A multi-center, randomized, controlled follow-up study was conducted at eight centers in China and approved by the ethical committees of each center. The patients were recruited from the general urological population between October 2015 and January 2018, and each patient signed an informed consent form prior to study participation. The study was designed using the recommendations of the Consolidated Standards of Reporting Trials (CONSRT) statement [18]. Figure 2 shows an overview of the procedures in this study.

All participants had a primary diagnosis of OAB and/or OAB symptoms, as demonstrated on a 5-day voiding diary, and had experienced previous treatments failure with at least one anticholinergic medication or could not tolerate more conservative treatments (e.g., pelvic floor, biofeedback, oral pharmacotherapy) [6, 12]. Treatment failure was defined as having a treatment discontinuation (treatment gap of ≥ 45 days) or switching anticholinergic therapy [19]. The definition of refractory to standard medical therapy was considered that subjects failed or could not tolerate at least one anticholinergic medication and have at least one anticholinergic medication not yet attempted. The details of the inclusion and exclusion criteria are provided in Table 1.

Study procedures

Based on the initial results, consisting of medical history, urodynamic testing, and baseline voiding diary information, a total of 84 OAB cases, meeting all inclusion criteria, were enrolled in the study. Participants underwent a two-stage implant procedure with the IPG implantation system requiring a 14-day test stimulation period. The first stage refers to the implanting of a permanent lead for testing the response to SNM under general anesthesia. Standardized electrode placement technique was described in great detail and used

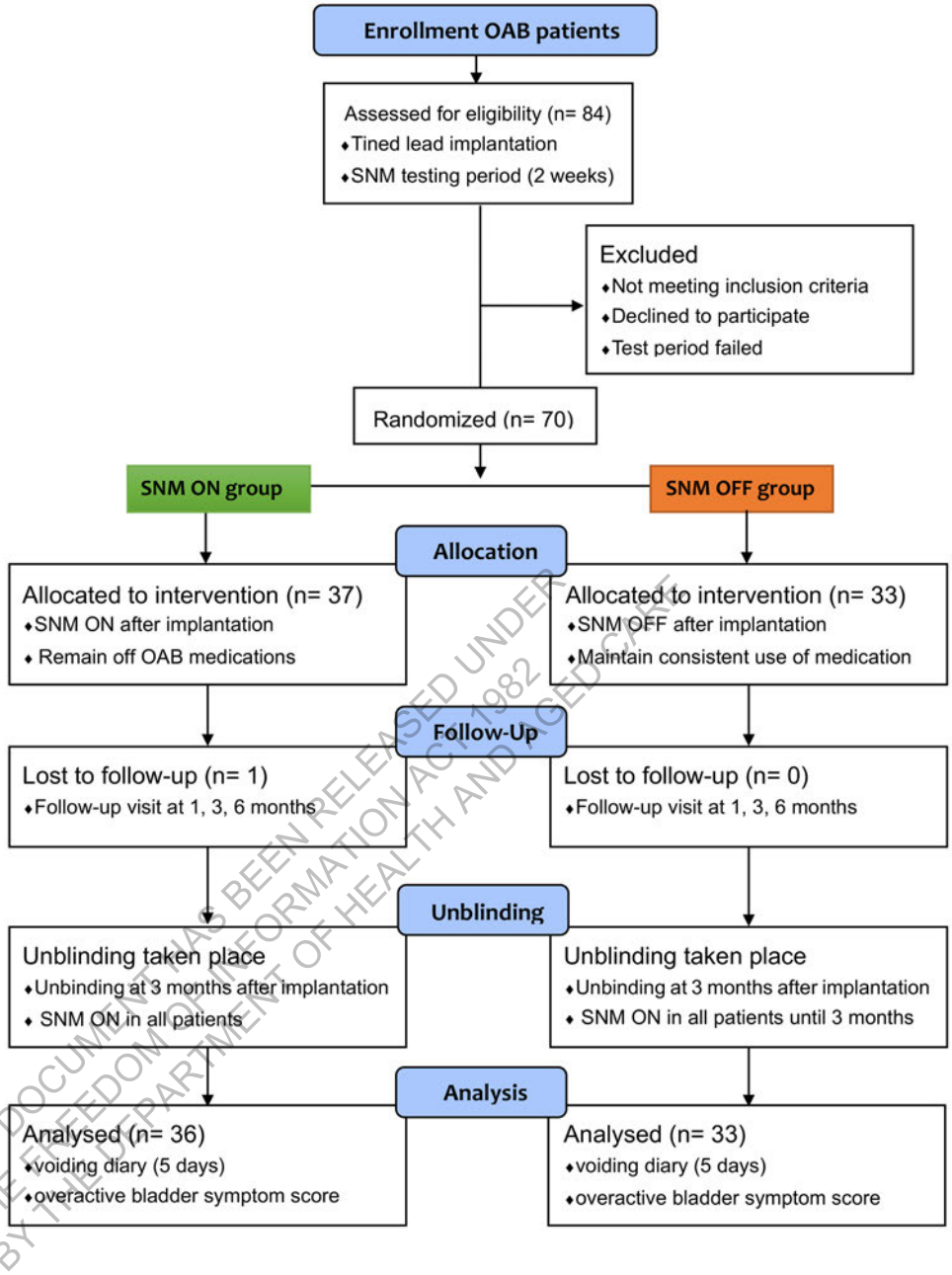

Fig. 2 Flowchart of the sacral neuromodulation clinical trial

the same procedure previously described for InterStim system [20]. Fluoroscopic guidance was used to implant the tined lead along the S3 sacra nerve root. It was recommended to give one dose of intravenous prophylactic antibiotics before SNM system implantation. In general, broad spectrum oral antibiotics were recommended for a period of 5–7 days after operation. Test stimulation success was considered as a $\geq 50\%$ improvement from baseline in key voiding variables [either in average voids/day or a return to normal voiding (< 8 voids/day) or average leaks/day] based on voiding diaries. After completion of test stimulation, those who met success criteria were implanted permanently with the neuromodulator. A pocket was made in the upper buttocks area to accommodate the IPG, and the tined lead was tunneled subcutaneously to the neurostimulator pocket. The neurostimulator and lead were connected and placed in the pocket. Then patients were randomized to treatment (stimulation ON) group or control (stimulation OFF) groups at a 1:1 ratio. An independent investigator performed the randomization and an online random number generator was applied to generate the random sequence (https://www.random.org/). All participants were unaware of the allocation.

After randomization, the stimulator was turned ON for each patient in the treatment group and the effectiveness of neuromodulation, as determined by the stimulation parameters, was optimized by an investigator not involved in

Table 1 List of selection criteria for patients with overactive bladder (OAB)

Inclusion criteria
Age greater than 16 years
Diagnosis of OAB as demonstrated on a 5-day voiding diary defined as ≥ 8 voids/day, and/or a minimum of 2 involuntary leaking episodes in a 72 h period
Refractory to standard medical therapy
≥100 mL bladder capacity with normal upper urinary tract
Good surgical candidate
Able to complete study documentation and return for follow-up evaluation
Exclusion criteria
Neurological conditions that may interfere with normal bladder function, including multiple sclerosis, spinal cord injury, or stoke occurs in the past 3 months
Primary stress urinary incontinence
Current symptomatic urinary tract infection (UTI)

evaluation of the clinical outcome. In the control group, the stimulator was turned OFF and patients followed their doctor's advice for medical therapy and maintained consistent use of any OAB medication (anticholinergic, antimuscarinic or tricyclic antidepressant) until 3 months. At the 3-month visit, unblinding was performed and the neuromodulator was turned ON in all patients.

Follow-up visits

All participants returned for follow-up visits post-implant at various time points, including 1, 3, and 6-month visits to assess initial response to therapy. A voiding diary, OABSS questionnaire, and medical history were collected to assess the response to treatment in each follow-up visit. Unscheduled follow-up visits were allowed as needed to adjust stimulation parameters to optimize therapy, either performed by conventional or remote programming. If both the patient and the physician felt remote programming was acceptable in lieu of an actual clinic visit, the patient's scheduled clinic appointment would be canceled. During follow-up visits, all adverse events (AEs), defined as device-related AEs, medication-related AEs or remote-programming related AEs, were documented.

Outcome measures

The primary outcome was the clinical therapeutic success rate of SNM, determined by voiding diary collected at the 3-month follow-up visit. The success rate was designated as participants with OAB symptoms had to demonstrate $a \geq 50\%$ improvement in average voids/day or average leaks/day compared with baseline values or a return to normal voiding frequency (< 8 voids/day). A participant was counted if she/he met the definition of clinical therapeutic success.

Secondary outcomes were the changes from baseline in mean number of leaks/day, voided volume/void, urinary urgency episodes per day, or voids/day over the first 6 months after implantation (1, 3, and 6-month assessments), based on the use of monthly 5-day voiding diary at each of those time points. Further, secondary outcomes including changes from baseline in the health-related quality of life and OABSS at the 3-month, and 6-month post-implant visits. Additionally, patient satisfaction and adverse events were evaluated.

To assess OAB-related quality of life (OABqol), changes through 6 months were calculated by comparing baseline values from follow-up visits. An interference question on the OABqol, "Overall, how much do your urinary symptoms interfere with your everyday life?", was measured on a scale, from 0 to 10 [21]. In addition, patient's satisfaction was evaluated by satisfaction questionnaire.

Sample size

The sample size was calculated using PASS version 12.1 software and determined by the clinical therapeutic success rate at the 3-month follow-up visit. We assumed that the success rate at the 3-month visit would be 30% in the control group and 60% in the treatment group. Success rates were estimated from previous studies with 76% for SNM and 49% for standard medical therapy [6]. The sample sizes were designated to provide 80% power for a one-tailed test, alpha = 0.025, comparison of 3-month OAB therapeutic success rates, with a 10% loss-to-follow-up rate. These calculations revealed that 68 individuals (34 per group) must be included.

Statistical analysis

Demographic and clinical data were collected at the time of presentation and analyzed using SAS version 9.4 software (version number: 11202165). All statistical tests were two-sided and a value of $P < 0.05$ was considered statistically significant. The continuous variables would be summarized with means and standard deviations (SD). A *t* test was used to assess comparisons between groups, and the Chi squared test or Fisher's exact test was applied for comparison of categorical variables.

Results

Demographic characteristics

Overall, 84 patients with OAB completed test stimulation and 70 patients received a full system implant, resulting

in an overall implant rate of 83%. All 70 patients with full system implants were randomized, 37 were allocated to the treatment group and 33 to the control group. Study outcome data remained blinded until the 3-month follow-up visit of the randomized participants was completed. 69 patients reached the 6-month post-implant visit, of whom 74% were females and 26% were males. Baseline demographics are presented in Table 2. There were no significant differences between the two groups in terms of demographics, baseline assessments, or medical history. Mean age with standard deviation (SD) at test stimulation was 54.31 ± 15.41 years (range 21.95–76.30). All patients were treated with long-term conservative therapy with a mean preadmission treatment period of 6.53 ± 5.30 years, which yielded poor efficacy or intolerance. Of the 70 patients, 60 (86%) had received pharmacological treatment, 30 (46%) had undergone surgical interventions, including intravesical endotoxin injection before the study.

Implant outcome

Efficacy at 3 months: results at the 3-month visit were available in 36 and 33 patients in the treatment and control groups, respectively. One patient in the treatment group was lost to follow-up. According to the statistical analysis, the average number of voids per day at baseline for patients was 28.27 ± 12.52, which decreased to 14.99 ± 7.98 at 3-month follow-up in the treatment group (Fig. 3a, $P < 0.001$). Compared to the control group, the treatment group significantly reduced the urinary urgency episodes (Fig. 3b, $P < 0.01$). Additionally, the voided volume per void increased post-implantation (Fig. 3c, $P < 0.05$), as well as the OABSS was visibly reduced than the control group (Fig. 4c, $P < 0.05$). Symptoms of urge incontinence at 3 months were significantly reduced in the treatment group (Fig. 3d, $P < 0.05$). In contrast, the control group patients showed no significant improvement in OAB symptoms at 3 months (Figs. 3, 4c). Changes from baseline in OAB symptoms between the two groups revealed great improvement in the treatment group, compared with the control group. As shown in Fig. 4, the analysis suggested an OAB therapeutic success rate of 72% in the treatment group, compared with 12% in the control group ($P < 0.001$).

Efficacy at 6 months: Voiding diaries were available for 69 patients at 6 months. As documented in the voiding diary analysis results, 33 patients in the control group exhibited a significant reduction in the average number of voids per day and the urinary urgency episodes per day, compared with baseline (Fig. 3a, b, $P < 0.05$). For the urinary incontinence patients, 9 patients in the control group and 11 patients in the treatment group showed great improvement in leaks. Over 6 months, both groups improved on the urinary symptoms, with the overall OAB therapeutic success rate was 69% and 61% in the treatment and control group, respectively. Further, there was no significant difference in the key voiding symptoms between the two groups. Therapeutic success rates and voiding variables suggest that the effectiveness of SNM therapy was sustained through 6-month post-implantation (Fig. 4a).

Changes from baseline in OABqol between the two groups suggested greater improvement in the treatment group, compared with control group, at the 3-month follow-up visit. A total of 78% of subjects in the treatment group reported an improved or greatly improved urinary symptom

Table 2 Baseline demographics and medical history

Demographic	Control group ($N = 33$)	Treatment group ($N = 37$)	P value
Gender			
Female	24 (72.73%)	27 (72.97%)	0.982
Male	9 (27.27%)	10 (27.03%)	
Age, years	50.36 ± 16.33	54.67 ± 15.16	0.254
Number of previous medications	1.69 ± 1.49	1.75 ± 1.32	0.728
Baseline voids/day	30.14 ± 17.30	28.27 ± 12.52	0.874
Baseline urgency of voids	2.77 ± 1.40	3.16 ± 1.33	0.244
Baseline void volume/void (mL)	87.19 ± 54.98	101.41 ± 53.41	0.219
Baseline leaks/day	1.42 ± 3.89	2.47 ± 5.94	0.281
OABSS domains			
Frequency	1.76 ± 0.50	1.86 ± 0.35	0.373
Nocturia	2.91 ± 0.29	2.78 ± 0.58	0.362
Urinary urgency	4.55 ± 0.90	4.32 ± 1.08	0.228
Urgency urinary incontinence	0.85 ± 1.72	1.19 ± 1.84	0.364
Total	10.06 ± 2.14	10.16 ± 2.18	0.711

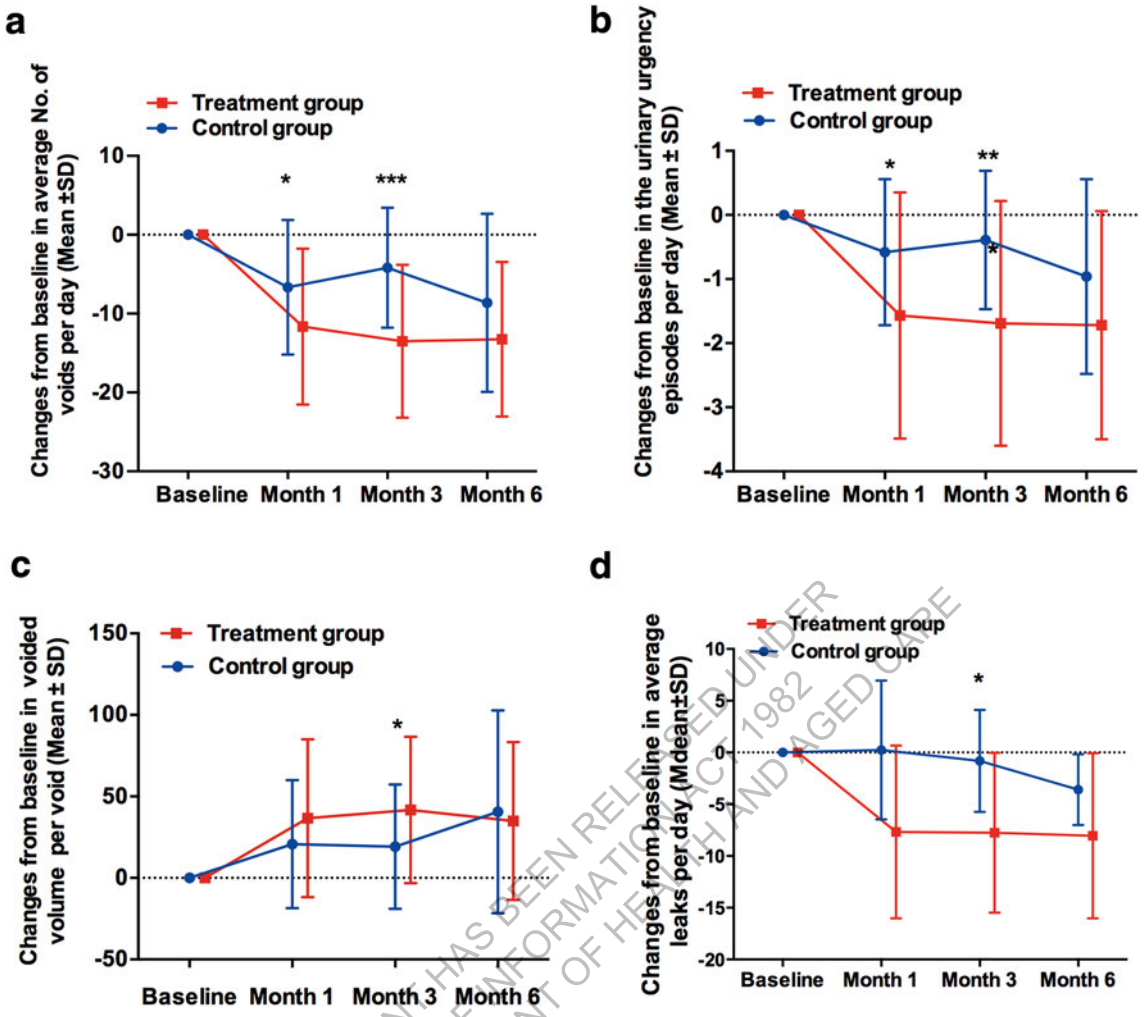

Fig. 3 Voiding symptoms in overactive bladder (OAB) symptoms between the treatment and control groups over time. **a** Changes from baseline in the average number of voids per day ($n=69$ all subjects, $n=33$ control group, $n=36$ treatment group). **b** Changes from baseline in the urinary urgency episodes per day ($n=69$ all subjects, $n=33$ control group, $n=36$ treatment group). **c** Changes from baseline in voided volume per void ($n=69$ all subjects, $n=33$ control group, $n=36$ treatment group). **d** Changes from baseline in the leaks per day ($n=20$ urinary incontinence subjects, $n=9$ control group, $n=11$ treatment group). $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ for significant difference between the treatment and control groups

interference score at 3 months, as compared to 6% in the control group (Fig. 4b, $P<0.001$). At the 6-month follow-up visit, all participants in each of the two groups showed greater improvement of urinary symptom interference score, and there was no significant difference between two groups (Fig. 4b, d).

Adverse events

Implant safety was evaluated through adverse event reports. During the 6-month follow-up visit, there were no unanticipated serious device-related AEs. Thirty-two events (25.71% of subjects) reported throughout the study period up to the 6-month visit. Specifically, device-related AEs occurred in 12.86% (9/70) of participants during the full system implant, comprising of implant site pain (2.86%, 2/70), undesirable change in stimulation (2.86%, 2/70), and loss of efficacy (7.14%, 5/70), resolved through device reprogramming. There were no serious AEs reported related to the implantable device. Further, no adverse events occurred related to remote programming.

Remote programming

According to our questionnaire results, postoperative follow-up burden was quantitatively evaluated by the average interval of clinical visits, travel distances, and general cost of a single follow-up. The mean travel distance from home to hospital is 1364.98 ± 764.93 km. 53% participants spend 500 RMB for each follow-up visit while 48% participants visit

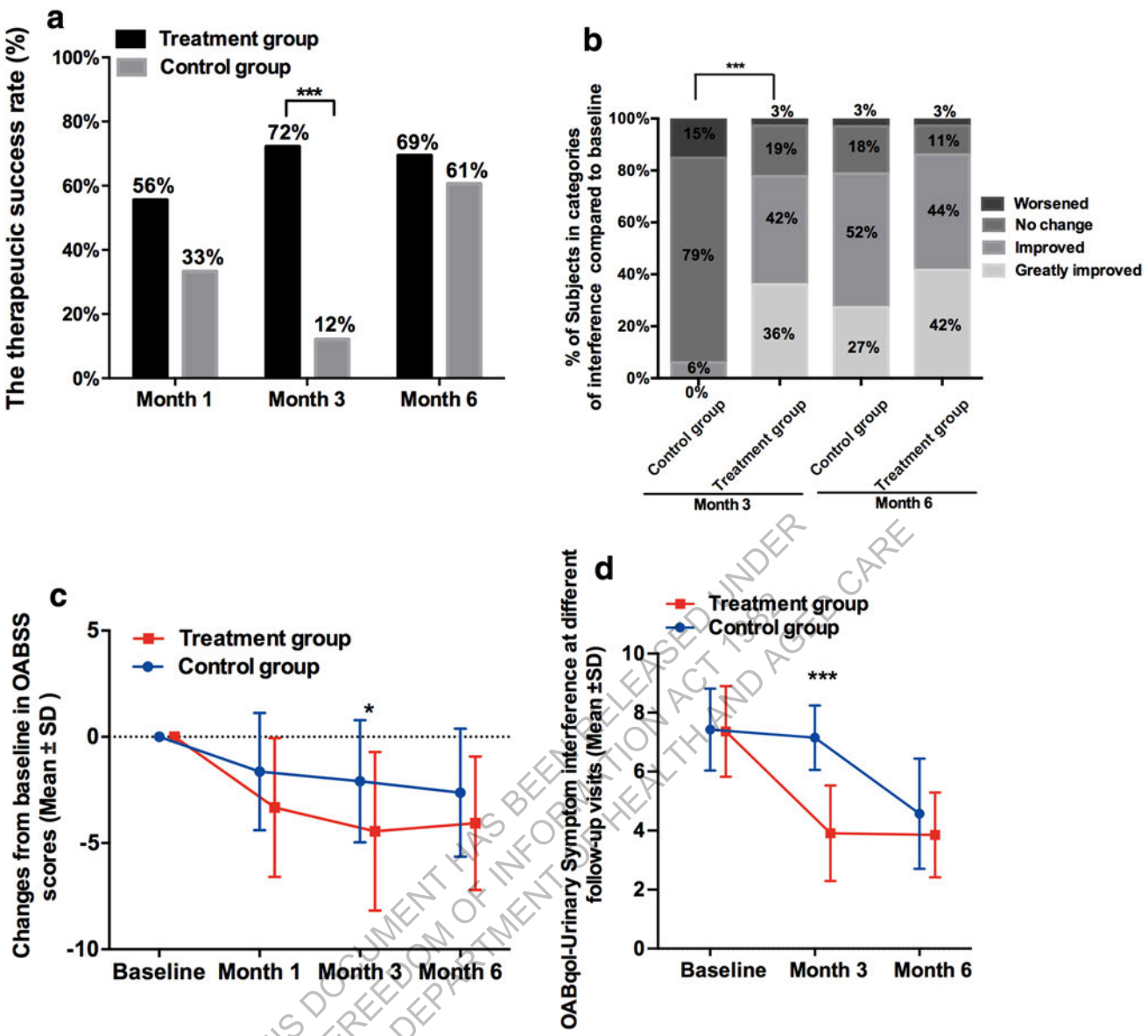

Fig. 4 Comparison of overall overactive bladder (OAB) therapeutic success rate and the overactive bladder quality of life (OABqol)-urinary symptom interference between the control and treatment groups. **a** OAB therapeutic success rate was defined as the percentage of patients that obtained $a \geq 50\%$ improvement in either of the key voiding diary variables, compared with baseline. **b** The difference between patient groups in the improvement of urinary symptom interference from baseline. **c** Changes from baseline in the OAB symptom score (OABSS). **d** OABqol-urinary symptom interference at different follow-up visits in OAB patients between the two groups. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ for significant difference between the treatment and control groups

hospital more than 4 times per month (Fig. 5a, b). Whereas patients selected remote programming, only need to stay at home with network coverage, regardless of distance.

During the follow-up visits, nearly 57 subjects received remote controlling, as well as conventional programming was performed in 70 patients to achieve maximal therapeutic benefit. Performance and parameter settings between this two programming methods were statistically indistinguishable (Fig. 5c, d). Complications related to remote-programming occurred in any session were zero. None of the patients experienced signal corruption during programming. With exception of a slightly delay of video signal existed in remote-programming session, there was no substantial difference in time commitment with programming conducted remotely or in-person. Indeed, time consume of the remote programming was more focused, with less tangential discussion. The mean frequency of setting up communication between patients and physicians was 1.68 ± 1.01 times. Interruptions occurred in remote programming were regarding to the limited speed Internet connectivity and improper operation, which could be

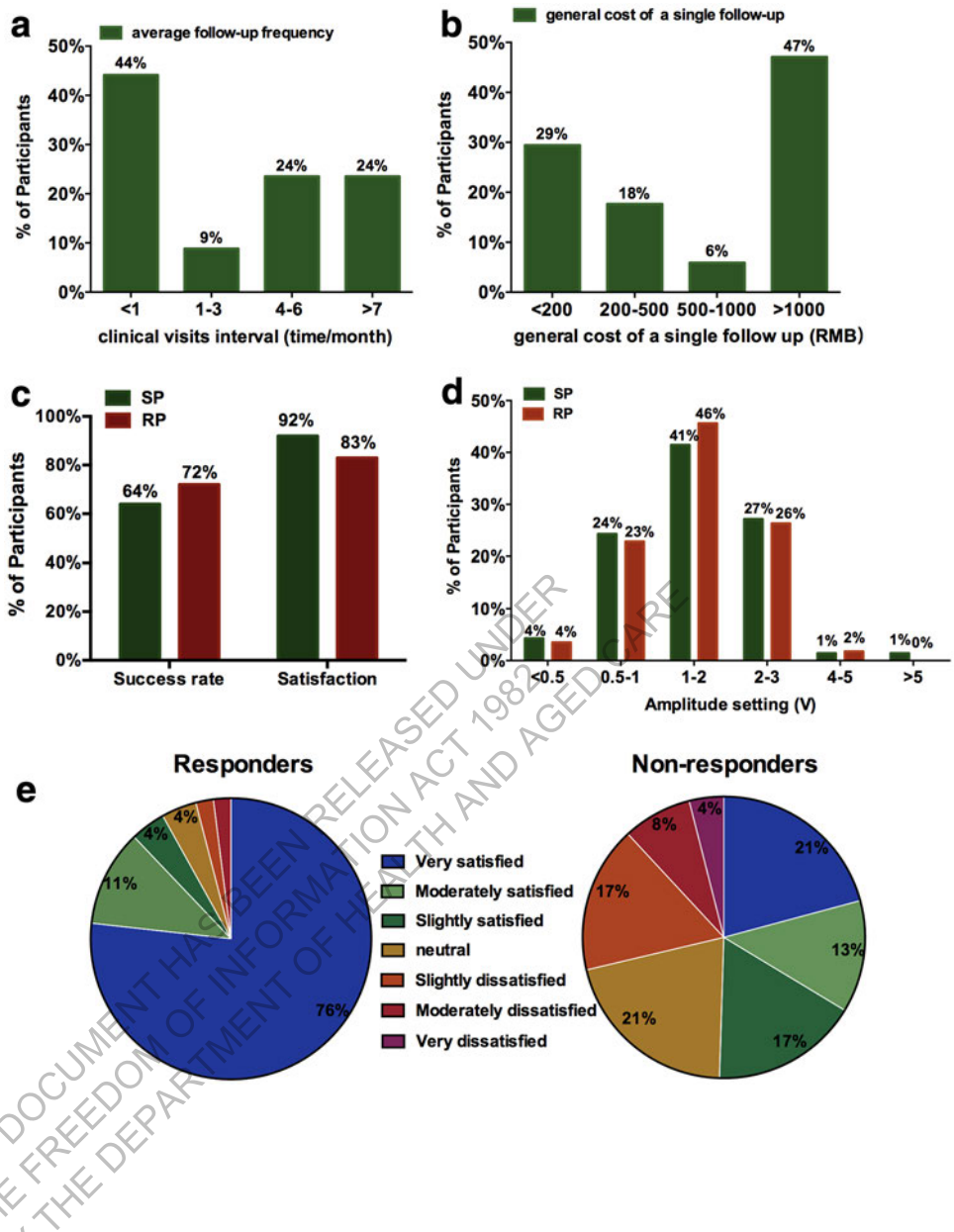

Fig. 5 Patient satisfaction with the remote-programming sacral neuromodulation (SNM) system. **a** The average total cost for each follow-up (RMB). **b** Patient's average interval of clinical visits per month. **c** The therapeutic success rate and satisfaction in patients referred to standard programming and remote-programming methods. *SP* standard programming, *RP* remote programming. **d** Amplitude settings in overactive bladder patients with different programming methods. *SP* standard programming, *RP* remote programming. **e** Patient satisfaction with the remote-programming sacral neuromodulation (SNM) system at 6 months. (left) Satisfaction for therapy responders—patients with ≥ 50% improvement in voiding symptoms ($n = 50$). (right) Satisfaction for therapy non-responders—patients with < 50% improvement in voiding symptoms ($n = 16$). ***$P < 0.001$

resolved through selecting good communication and optimizing procedures.

Nearly all patients and physician programmer expressed a high degree of satisfaction with the remote-programming sessions. Patients preferred the remote programming and reported a 92% satisfaction, whereas 83% patients agreed with conventional programming (Fig. 5c). Overall, among the 69 implanted patients, 77% were satisfied with their clinical therapy, and when analyzed for therapy responders, 91% of patients were satisfied with their therapy. For the patients who did not meet the definition for therapeutic success, 21% of patients remained very satisfied with SNM therapy (Fig. 5e).

Discussion

To date, OAB remains a great challenge owing to the available treatments which may either exhibit moderate efficacy or be highly invasive. Consequently, a successful and efficacious long-term therapy is extremely important for the management of refractory OAB. This study is the first randomized controlled study in humans to compare clinical outcomes from a SNM stimulation ON group against a control group for the treatment of OAB. The data from this 6-month phase of the study provided strong scientific

evidence for the benefits of BetterStim system among OAB patients. The overall OAB therapeutic success rate demonstrated high efficiency of SNM for OAB patients after 6 months of treatment. While long-term durability of BetterStim SNM system needs to follow-up until 5 years after implantation. The efficacy of SNM revealed in this trial is comparable with previously reported results of other SNM device [6, 9, 12, 22]. When compared to the patient population of the InSite trial, this cohort of all patients was considered to have severe OAB ($\geq$ 11 voids/day) with a mean of 29.15 voids per day at baseline, which confirms that SNM is equally effective regardless of severity of OAB symptoms [23]. Of the 69 patients with implants, 43 (62%) no longer required combination therapy with medication to improve their OAB symptoms. Besides the objective differences, this study also revealed a significant improvement in subjective measurements. Sustained quality of life improvement was reported from baseline to the 3-month follow-up visit in terms of urinary symptom interference in the treatment group, compared with the control group. Additionally, the high rate of patient satisfaction suggests that patients would benefit from this BetterStim system at 6-months. Overall, these findings reinforce the efficiency of BetterStim system for OAB treatment.

The reported complication rate in this study is significantly lower than previously published studies [9, 12, 24], but must be considered as a matter of therapy evaluation. This may be related to the technologies employed during this study, including the application of tined lead and fluoroscopic guidance for implanting the lead. No serious device-related AE and unanticipated adverse events were reported. The most common device-related AE reported was loss of efficacy in this study. This type of event occurred within 6 months of implant in 4.00% of patients in the InSite study in 7.14% of subjects to date in this study. In this study, the rate of implant site pain was one-third of what was represented in the InSite trial (2.86% vs 8.50%, respectively). Undesirable change in stimulation was also considerably lower in the current trial compared to InSite trial (2.86% vs 10.2%). In both studies, these events were often resolved by medications or complex reprogramming [12, 25]. These data suggest that this novel BetterStim system is safe. Long-term follow-up is needed to determine if the BetterStim system impacts AEs rates.

Notably, patients undergoing SNM therapy often must travel significant distances, which represent a considerable investment on their part of time for a postoperative programming. The ideal solution to the outlined issues lies in wireless and remote-programming technology [26]. With this technology, the need for patients normally required back to hospital in-person is eliminated, thus obviously minimize inconvenience and costs associated with traveling for an in-person clinic visit. Remote programming of implanted SNM system is possible via wireless communication function, thereby enabling patients to receive the same treatment outcomes in their own home as in the hospital. Additionally, the BetterStim system has software controls such that parameter settings would be restored if the signal interrupts. Data for programming from all patients can be stored and analyzed for further investigation and optimization. Therefore, it may revolutionize the management of post-implant patients and allow the development of an applicable and reliable alternative within the market, especially in developing countries.

Although it is vital to report on the efficacy and safety of this novel BetterStim system in the setting of a clinical trial, some limitations need to explored. No previous beta3 adrenoceptor agonist monotherapy and/or its combination with anticholinergic drugs were applied for refractory OAB patients, largely due to beta3 adrenoceptor agonist was not approved for clinical use in China during the trial period. In addition, the definition of refractory OAB was not clearly stated in the inclusion criteria, though all clinical centers recruited patients in terms of suggestion that subjects failed or could not tolerate at least one anticholinergic and have at least one anticholinergic medication not yet attempted. Furthermore, this trial provided 6-month follow-up data without long-term results. This study is an ongoing trial, the quality and long-term duration of treatment benefits will continue to be confirmed. Further investigations will focus on the molecular mechanisms underlying the efficacy of sacral neuromodulation, specifically, the mechanisms by which neuromodulation may affect the functioning of bladder, urethra, sphincter, and other organs that are dominated by the sacral nerve.

Conclusions

This is the first multicenter, prospective, randomized, controlled study testing the efficacy of BetterStim system in OAB subjects. In summary, results from the present study provide strong evidence that this novel remote-programmed SNM system (PINS, Beijing, China) is safe and effective for patients with refractory OAB symptoms. Importantly, our data suggest that remote programming can be safely used as a viable option for the conventional postoperative clinic visit with a high degree of patient satisfaction.

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Author contributions JYW: protocol/project development, data collection and management, data analysis, and manuscript writing. YGZ: protocol/project development, data collection and management, data analysis, and manuscript writing. LML: protocol/project development, data collection and management, data analysis, and manuscript writing.

PZ: protocol/project development, data collection and management, and data analysis. GQC: protocol/project development and data collection and management. YL: protocol/project development and data collection and management. YZ: protocol/project development and data collection and management. ZQW: protocol/project development and data collection and management. LLM: protocol/project development and data collection and management. XJT: protocol/project development and data collection and management. BKS: protocol/project development, data collection and management. ZHX: protocol/project development and data collection and management. WZ: protocol/project development and data collection and analysis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval All the procedures performed involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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- Proprietary 5th generation battery chemistry manufactured exclusively by Medtronic
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*Please note: This device is currently under review for TGA & WAND certification and is not yet commercially available in ANZ.

1. Under expected therapy settings and telemetry use.
2. Please see System Eligibility, Battery Longevity, Specifications manual for battery longevity estimate

InterStim™ X* System

System Elements

Implantable Neurostimulator

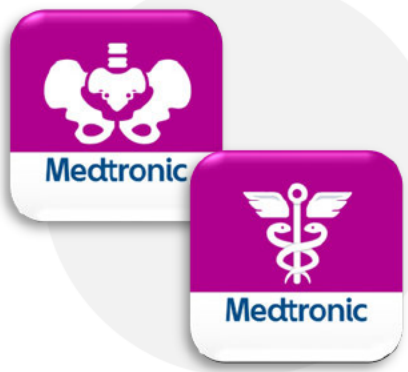
- Model **97800** InterStim™ X*

Smart Programmer

- Model **TH90Q02*** Kit
  - Model HH9021SNM Handset
  - Model TM90Q0 Communicator

Therapy Apps

- Model **A51300** Clinician
- Model **A52300** My Therapy (patient)



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InterStim™ X Sacral Neuromodulation System

InterStim™ X System

Device Description

The InterStim X system for is an implantable programmable neuromodulation system that delivers electrical stimulation to the sacral nerve for patients with incontinence. The system includes:

- an implantable neurostimulator (INS)
- an implantable lead, and
- a programmer kit, containing a handset (loaded with clinician and patient software applications) and a communicator (which allows the handset to communicate with the neurostimulator).

The clinician software application is used to configure and maintain the patient's therapy through adjustment of the available therapy parameters (amplitude, rate, pulse width, cycling, SoftStart/Stop, and electrode configuration) and the creation of programs which consist of a specific set of values for each of the therapy parameters. The patient software application is used to maintain their therapy through stimulation intensity adjustment and program selection. The programs are pre-set by the clinician.

Medtronic InterStim II (comparator device) uses the Delta 26H2 battery and the InterStim X has an updated Delta 26H3 battery. The difference between these batteries is the internal chemistry (type of fluorinated carbon, electrolytes, and the ratio of fluorinated carbon to silver vanadium oxide).

The Delta 26H3 battery has better power capacity, enabling the InterStim X INS to sustain higher current uses. The average battery life of the InterStim™ II (recharge-free) is 3 to 5 years and the battery life of the InterStim™ X is 10 years.

Increased device longevity results in a reduction in number of replacement surgeries, thus reducing the health system costs of replacement devices, replacement surgery and potentially additional risks to patients associated with surgical procedures.

Benefit Request: Medtronic InterStim™ X System

The purpose of this submission is to provide information to support the request for a new sub group with a benefit for the Medtronic InterStim X System proportionate to its extended battery life. The proposed benefit for the InterStim X of s47G is based on both the demonstrated health system savings (primarily private health insurance benefit payment savings) through increased device longevity and the established Prostheses List (PL) benefit for rechargeable neurostimulator devices.

Economic Model

s47G

s47G

to demonstrate that InterStim X's 10-year battery life leads to cost savings over a 20-year time horizon when compared to InterStim II.

Cost inputs were sourced from literature review and cost inputs were obtained from the March 2023 PL, MBS Online, Private Health Data Bureau and Hospital Casemix Protocol Data. s47G

These cost savings would accrue to the Australian healthcare system due to fewer replacement surgeries. These health system cost savings include reduced private health insurance (PHI) benefit expenditure from hospital policies on private hospital admissions including PL benefit payments for devices. In addition to the health system cost savings, fewer replacement surgeries and lower out of pocket costs related to PHI excess and medical gap payments are also an important patient relevant outcome.

InterStim™ X System - Neurostimulator

InterStim™ X System – Neurostimulator is clinically equivalent to the comparator InterStimII Neurostimulator.

	Device in application	Comparator	Analysis	References
Billing code	TBC	MC755	N/A	Mar 2023 PL
Benefit	s47G	$9,073	Same as nominated comparators	Mar 2023 PL
Product Name	InterStim X System – Neurostimulator	InterStim II Neurostimulator	N/A	Mar 2023 PL
Description	Recharge-free implantable neurostimulator	Model 3058 neurostimulator	N/A	Mar 2023 PL
Image			N/A	Product brochure
Intended use	The InterStim system is an implantable programmable neuromodulation system that delivers electrical stimulation to the sacral nerve. The neuromodulation system can be implanted either unilaterally or bilaterally.	The InterStim system is an implantable programmable neuromodulation system that delivers electrical stimulation to the sacral nerve. The neuromodulation system can be implanted either unilaterally or bilaterally.	Same as nominated comparator	IFU
Intended indication	indicated for the management of the following chronic intractable (functional) disorders of the pelvis and lower urinary or intestinal tract: overactive bladder, fecal incontinence, and non-obstructive urinary retention.	indicated for the management of the following chronic intractable (functional) disorders of the pelvis and lower urinary or intestinal tract: overactive bladder, fecal incontinence, and non-obstructive urinary retention.	Same as nominated comparator	IFU
Grouping	05.07 - Sacral Neuromodulation 05.07.01 - Primary Cell Pulse Generator (non-rechargeable)	05.07 - Sacral Neuromodulation 05.07.01 - Primary Cell Pulse Generator (non-rechargeable)	Same as nominated comparator	Mar 2023 PL

	Device in application	Comparator	Analysis	References
	New product grouping	*Existing product grouping*		
Size	One size only	Weight 22g	N/A	Mar 2023 PL
ARTG	DV-2023-DA-01233-1	391141	N/A	TGA Certificate & DV number
GMDN	36175 Stimulator, electrical, neuromuscular, incontinence, implantable	36175 Stimulator, electrical, neuromuscular, incontinence, implantable	Same as nominated comparator	TGA Certificate & DV number
Material	Titanium, Thermoplastic Polyurethane	Titanium, Thermoplastic Polyurethane	Same as nominated comparator	IFU
Design	Designed to deliver stimulation as part of a neurostimulation system for sacral neuromodulation therapy	Designed to deliver stimulation as part of a neurostimulation system for sacral neuromodulation therapy	Same as nominated comparators	IFU
Specifications	Single sized implant that delivers electrical stimulation to the sacral nerve.	Single sized implant that delivers electrical stimulation to the sacral nerve.	Same as nominated comparators	IFU

PL = Protheses List; IFU = instructions for use; TGA = Therapeutic Goods Administration; ARTG = Australian Registered Therapeutic Good; GMDN = Global Medical Device Nomenclature.

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Medtronic

Limited Warranty Statement

For Medtronic Interstim™ X Neurostimulator

ANZ Customers Only

April 2023

A. Medtronic offers this Limited Warranty to provide the following assurance to a patient who receives a Medtronic Interstim™ X Neurostimulator ("**Neurostimulator**"). You also have Consumer Rights if the device is sold in Australia or New Zealand, as outlined below.

(1) Should the Neurostimulator fail to function within normal tolerances due to a defect in materials or workmanship within a period of ten (10) years, commencing with the date of implantation, Medtronic will at its option: (a) issue a credit to the purchaser of the replacement Neurostimulator equal to the Purchase Price, as defined in Subsection (2) below, against the purchase of any same Neurostimulator requested as its replacement, or, (b) provide a functionally comparable replacement Neurostimulator at no charge.

(2) As used in this Limited Warranty, Purchase Price means the lesser of the net invoiced price of (a) the original Neurostimulator or (b) the current functionally comparable, or replacement Neurostimulator.

B. To qualify for this Limited Warranty, all of these conditions must be met:

(1) The Neurostimulator must have been purchased and implanted in Australia or New Zealand.

(2) The Neurostimulator must be implanted prior to its "Use By" date.

(3) The Neurostimulator must be used in conjunction with components compatible with the Medtronic Interstim X Neurostimulator System.

(4) The replaced Neurostimulator must be returned to Medtronic within thirty (30) days of explantation and shall become the property of Medtronic.

(5) The Neurostimulator must be used in accordance with the labelling and instructions for use provided with the Neurostimulator.

(6) The battery of the Neurostimulator must have been handled in accordance with the physician and patient manuals, especially the battery must not have been over discharged.

C. This Warranty is limited to its express terms. In particular:

(1) Except as expressly provided by this Limited Warranty, MEDTRONIC IS NOT RESPONSIBLE FOR ANY DIRECT, INCIDENTAL OR CONSEQUENTIAL DAMAGES BASED ON ANY DEFECT, MALFUNCTION OR FAILURE OF THE NEUROSTIMULATOR TO FUNCTION WITHIN NORMAL TOLERANCES WHETHER THE CLAIM IS BASED ON WARRANTY, CONTRACT, NEGLIGENCE, STRICT LIABILITY, OTHER TORT OR OTHERWISE.

(2) This Limited Warranty is made only to the patient in whom the Neurostimulator was implanted.

(3) The exclusions and limitations set out above are not intended to, and should not be construed so as to contravene mandatory provisions of applicable law. If any part or term of this Limited Warranty is held to be illegal, unenforceable or in conflict with applicable law by a court of competent jurisdiction, the validity of the remaining portions of the Limited Warranty shall not be affected, and all rights and obligations shall be construed and enforced as if this Limited Warranty did not contain the particular part or term held to be invalid. This Limited Warranty gives the patient specific legal rights. The patient may also have other rights that vary from country to country or from jurisdiction to

jurisdiction.

(4) No express warranty to the patient shall extend beyond the applicable period specified in Section A above.

(5) No person has any authority to bind Medtronic to any representation, condition, or warranty, except this Warranty.

YOUR CONSUMER RIGHTS – ANZ CUSTOMERS AND PATIENTS

The language used above is in addition to, and should not be construed to, detract from any rights and remedies that a consumer may have under Australian and New Zealand consumer legislation (**Your Consumer Rights**). Any exclusion of direct, incidental, consequential or other damages and other warranties (including express or implied warranties of merchantability, fitness for purpose etc.) referred to above will not affect Your Consumer Rights.

For Australia: "*Our goods come with guarantees that cannot be excluded under the Australian Consumer Law. You are entitled to a replacement or refund for a major failure and for compensation for any other reasonably foreseeable loss or damage. You are also entitled to have the goods repaired or replaced if the goods fail to be of acceptable quality and the failure does not amount to a major failure*."

Special Notice for Neurostimulators

Neurostimulators once implanted are implanted in the extremely hostile environment of the human body. This environment places severe demands on its design and function.

Reasons for failure of the Neurostimulator include, but are not limited to: body rejection phenomena; change in performance characteristics due to component changes or failures; unusual physiological variations in patients; medical complications; migration; or erosion of the area around the Neurostimulator.

In addition, despite the exercise of all due care in design, component selection, manufacture, and testing prior to sale, the Neurostimulator may be damaged before, during, or after implantation by improper handling, by uses not described in the user manual, or by other intervening acts.

The Neurostimulator includes a non-separable power source which will ultimately cease to function due to exhaustion or premature failure, thereby necessitating removal of the Neurostimulator.

Consequently, no representation or warranty is made that failure or cessation of function of the Neurostimulator will not occur, or that the body will not react adversely to its implantation.

No representation is made that any one Neurostimulator will last the entire lifetime of any user or for any specific length of time. Inherent uncertainties regarding the longevity of the components make any such assurance impossible.

For further information regarding safety information or possible complications resulting from the use of a Neurostimulator System, consult the Neurostimulator manuals.

Medtronic

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Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Public Summary

Summary for ARTG Entry:	421914	Medtronic Australasia Pty Ltd - InterStim X Model 97800 - Implantable incontinence-control electrical stimulation system pulse generator

ARTG entry for	Medical Device Included Class III
Sponsor	Medtronic Australasia Pty Ltd
Postal Address	PO Box 945, NORTH RYDE BC, NSW, 1670 Australia
ARTG Start Date	15/09/2023
Product Category	Medical Device Class III
Status	Active
Approval Area	Medical Devices

Conditions

- The inclusion of the kind of device in the ARTG is subject to compliance with all conditions placed or imposed on the ARTG entry. Refer Part 4-5, Division 2 (Conditions) of the Therapeutic Goods Act 1989 and Part 5, Division 5.2 (Conditions) of the Therapeutic Goods (Medical Devices) Regulations 2002 for relevant information.
- Breaching conditions of the inclusion related to the device of the kind may lead to suspension or cancellation of the ARTG entry; may be a criminal offence; and civil penalties may apply.

Manufacturers

Name	Address
Medtronic Inc	710 Medtronic Parkway Minneapolis, MN, 55432 United States Of America

Products

1 . InterStim X Model 97800 - Implantable incontinence-control electrical stimulation system pulse generator

Product Type	Single Device Product	**Effective Date**	15/09/2023
GMDN	61391 Implantable incontinence-control electrical stimulation system pulse generator		
Functional Description	The implantable neurostimulator (INS) is a programmable device that delivers stimulation through a lead. Programmable parameters include amplitude, pulse width, rate, and cycling		
Intended Purpose	The implantable neurostimulator generates electrical pulses and delivers stimulation through one lead as part of a neurostimulation system for sacral neuromodulation therapy		
Variant information	Nil variant (as 1 device) N/A		

Specific Conditions

No Specific Conditions included on Record

s47G Clinical Assessment

s47C

s47F 27 June 2023

COMMITTEE–IN–CONFIDENCE

General Surgery Expert Clinical Advisory Group

Agenda item 5.2 – MDHTP Prescribed List new applications for discussion

Application Number	s47G s22
Sponsor	Medtronic Australasia Pty Ltd
Product Name	InterStim X System - Neurostimulator
Description	Recharge-free implantable neurostimulator
Size	One size only
Catalogue Numbers	*Implantable Neurostimulator Model 97800* *InterStim™ X** 97800 
ARTG	DV-2023-DA-01233-1, dd 18/01/2023
s22	s22
Proposed Grouping	05 - Urogenital 05.07 - Sacral Neuromodulation 05.07.01 - Primary Cell Pulse Generator s22

	(non-rechargeable) New sub-group: Extended Battery Life	s22
Benefit	s47G	
Comparator	MC755 - InterStim II Neurostimulator 05.07.01 - Primary Cell Pulse Generator (non-rechargeable) Benefit: $9,073	
Clinician assessment s47F	Applications are suitable	
	s47C	
	s22	
	s47C	
Department comment	For discussion	
	The sponsor applied to list the Urogenital Sacral Neuromodulation Pulse Generator in the new sub-group, claiming the device has longer battery life. There are currently 2 groups: 05.07.01 - Sacral Neuromodulation - Primary Cell Pulse Generator (non-rechargeable), benefit $9,073 and 05.07.05 -- Sacral Neuromodulation Rechargeable Pulse Generator, benefit s47G . s47G s47C	

s22

s47G s22 *- InterStim X System – Neurostimulator (Medtronic Australasia Pty Ltd)*

The devices are the Sacral Neuromodulation Primary Cell Pulse Generator and the s22 , for treatment of urinary incontinence.

The Generator in application s47G has a non-rechargeable battery but with the extended life, and the sponsor applied to list it in the new sub-group Extended Battery Life with the benefit s47G that is the same as the benefit payable for group 05.07.05 for the Sacral Neuromodulation rechargeable neurostimulators.

s47C

s47C

It was further noted that the benefit for the re-rechargeable neurostimulators was estimated based on the battery life of 10 year. The sponsor provided the manufacturer's warranty statements declaring that the expected life of the subject device (Medtronic Interstim™ X Neurostimulator) is also 10 years.

s47C

Members recommended the subject device is suitable for listing in the new sub-group 05.07.01.01 – Urogenital – Sacral Neuromodulation – Primary Cell Pulse Generator (non-rechargeable) - Extended Battery Life, with benefit s47G .

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Advice to sponsor

s47G

General Surgery Expert Clinical Advisory Group (GSECAG) assessed the application and noted that the device has a non-rechargeable battery but with the extended life, and the sponsor applied to list it in the new sub-group Extended Battery Life with the benefit s47G that is the same as the benefit payable for group 05.07.05 for the Sacral Neuromodulation rechargeable neurostimulators.

s47C

It was noted that the benefit for the re-rechargeable neurostimulators was estimated based on the battery life of 10 year, and according to the manufacturer's warranty statements the expected life of the subject device (Medtronic Interstim™ X Neurostimulator) is also 10 years.

Members recommended the subject device is suitable for listing in the new sub-group 05.07.01.01 – Urogenital – Sacral Neuromodulation – Primary Cell Pulse Generator (non-rechargeable) - Extended Battery Life, with benefit s47G

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Application Number	s47G
Sponsor	Medtronic Australasia Pty Ltd
Product Name	InterStim X System - Neurostimulator
Description	Recharge-free implantable neurostimulator
Size	One size only
Catalogue Numbers	*Implantable Neurostimulator Model 97800 InterStim™ X** 97800 
ARTG	DV-2023-DA-01233-1, dd 18/01/2023

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Proposed Grouping	05 - Urogenital 05.07 - Sacral Neuromodulation 05.07.01 - Primary Cell Pulse Generator (non-rechargeable) New sub-group: Extended Battery Life
Benefit	s47G
Comparator	MC755 - InterStim II Neurostimulator 05.07.01 - Primary Cell Pulse Generator (non-rechargeable) Benefit: $9,073
GSECAG Assessment	Devices are suitable in the sponsor's proposed sub-groups
	The Generator in application s47G has a non-rechargeable battery but with the extended life, and the sponsor applied to list it in the new sub-group Extended Battery Life with the benefit s47G that is the same as the benefit payable for group 05.07.05 for the Sacral Neuromodulation rechargeable neurostimulators. s47C s47C the expected life of the device with the standard non-rechargeable battery is 6-7 years [there is currently 1 billing code MC755 for InterStim II Neurostimulator, listed in group 05.07.01 - Primary Cell Pulse Generator (non-rechargeable), benefit $9,073]. It was further noted that the benefit for the re-rechargeable neurostimulators was estimated based on the battery life of 10 years. The sponsor provided the manufacturer's warranty statements declaring that the expected life of the subject device (Medtronic Interstim™ X Neurostimulator) is also 10 years. The expected life of the subject device is considered to be comparable with the expected life of the rechargeable devices listed in group 05.07.05. GSECAG recommended the subject device is suitable for listing in the new sub-group 05.07.01.01 – Urogenital – Sacral Neuromodulation – Primary Cell Pulse Generator (non-rechargeable) - Extended Battery Life, with benefit s47G s22
Department comment	Devices are suitable in the sponsor's proposed sub-groups
	The sponsor applied to list the device in the new sub-group, that has been found to be acceptable. No further comment

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s47G *- InterStim X System - Neurostimulator (Medtronic Australasia Pty Ltd)*
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The device in application s47G is sacral neurostimulator with a non-rechargeable but extended life battery. The sponsor applied to list the device in 05.07.01 -Urogenital – Sacral Neuromodulation – Primary Cell Pulse Generator (non-rechargeable) - New sub-group Extended Battery Life, with benefit s47G .

The standard non-rechargeable battery is 6-7 years [there is currently 1 billing code MC755 for InterStim II Neurostimulator, listed in group 05.07.01 - Primary Cell Pulse Generator (non-rechargeable), benefit $9,073]. The benefit s47G payable for the re-rechargeable neurostimulators was estimated based on the battery life of 10 years. The sponsor provided the manufacturer's warranty statements declaring that the expected life of the subject device (Medtronic Interstim™ X Neurostimulator) is also 10 years, i.e. the expected life of the subject device is considered to be comparable with the expected life of the rechargeable devices listed in group 05.07.05.

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TO: s22 , A/g Assistant Secretary
Prostheses List Reform Taskforce
Technology Assessment and Access Division

GRANTING NEW AND APPROVAL OF AMENDMENT, EXPANSION APPLICATIONS – 1 NOVEMBER 2023 LIST OF MEDICAL DEVICES AND HUMAN TISSUE PRODUCTS

Purpose

To seek your decision to:

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2. **GRANT** s22 new applications for listing medical devices and human tissue products on the Prescribed List of Medical Devices and Human Tissue Products (Prescribed List)

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Issues

The *Private Health Insurance Act 2007* (the Act) is the primary legislation regulating private health insurance, including the existing arrangements requiring private health insurers to pay benefits to patients with appropriate private health insurance policies for approved medical devices and human tissue products received as part of hospital and hospital substitute treatment, for which a Medicare benefit is payable.

The Act has been amended and these arrangements took effect from 1 July 2023[1]. Specifically, the legislative amendments gave effect to the change to the name of the Rules made under the Act from the *Private Health Insurance (Prostheses) Rules* (Prostheses Rules) to the *Private Health Insurance (Medical Devices and Human Tissue Products) Rules* (MDHTP Rules). The Prescribed List (PL) is the Schedule of the MDHTP Rules.

The *Private Health Insurance (Medical Devices and Human Tissue Product) Rules (No. 1) 2023* (MDHTP Rules No 1) is the legislative instrument that set up the requirements for provision of minimum benefits for medical devices and human tissue products. Consistently with the previously agreed administrative practice for the Prostheses List, the MDHTP Rules are made 3 times per year with commencement on 1 March, 1 July and 1 November each year. The expected date for commencement of the next MDHTP Rules is 1 November 2023.

Under the existing PL arrangements, the sponsor (medical device company or human tissue processing facility) needs to submit an application (by a specified cut-off date) and pay a respective application fee (where applicable) to the Department in order to apply for a medical device or human tissue product to be listed on the PL (*new application*) or an existing PL billing code to be amended (*amendment, expansion and compression application*). Applications have been submitted via the web-based Prostheses List Management System (PLMS) that is also currently used by the Department to manage workflow, track applications, and produce reports and the PL documents.

The applications (provided for consideration under this Minute) had been submitted before 1 July 2023, i.e. sponsors were required to pay the application fee of $600, effective at that time. The changes in the MDHTP Rules relating to cost recovery fees [standard application fee of $1,370, clinical assessment fee, and economic assessment] do not have retrospective effect [and only apply to the applications received on or after 1 July 2023 and will be assessed for 1 July 2024 PL].

[1] *Private Health Insurance Act 2007*, Compilation No. 36, C2023C00107, https://www.legislation.gov.au/Details/C2023C00107

According to section 72-10 of the Act, the MDHTP Rules must only list a kind of medical device or human tissue product on the PL, if the Minister has granted the PL application. The power and functions under the Act have been delegated to SES Band 2 and SES Band 1 staff in the Health Resourcing Group [refer to the *Private Health Insurance Act (Minister) Delegation (No. 3) 2023* (Instrument of Delegation) at D23-3128533.] According to the advice from the Legal and Assurance Division (LAD), this Instrument is current for making granting decisions required under this Minute.

As the A/g Assistant Secretary, Prostheses List Reform Taskforce, **you have delegation to grant or not to grant the new applications and approve amendment and expansion applications** under section 72-10 of the Act. Your decisions on granting and not granting new applications and approval of amendment and expansion applications are required.

Section 28 of the MDHTP Rules provides that in making a decision under subsection 72-10 of the Act on whether to grant an application, the Minister may have regard to a recommendation or advice from the Medical Devices and Human Tissue Advisory Committee (MDHTAC). Majority of the applications presented in this Minute have been considered by the MDHTAC. Although some older applications were considered by the former Prostheses List Advisory Committee (PLAC). The advice from both of these committees has informed the recommendations presented to you in this Minute. You may agree with the recommendations or make decisions based on your own deliberation.

Under subsection 72-10(4) of the Act you, as the Minister's delegate, must inform the applicant in writing of the decision whether or not to grant the application. The sponsors will be advised of the granting decisions for their applications.

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Background

The PL is the Schedule to the MDHTP Rules. There are 4 parts of the Prescribed List:

Schedule, Prescribed List – Part A
Schedule, Prescribed List – Part B
Schedule, Prescribed List – Part C
Schedule, Prescribed List – Part D

Under the current administrative arrangements, **Part A** of the PL covers surgically implantable medical devices, medical devices essential for implanting medical devices on the PL or medical devices essential for ongoing functioning of medical devices on the PL. There are 13 categories of devices in this part [Ophthalmic; Ear, Nose and Throat; General Miscellaneous; Neurosurgical; Urogenital; Specialist Orthopaedic; Plastic and Reconstructive; Cardiac; Cardiothoracic; Vascular; Hip; Knee; and Spinal].

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Sponsors submit ***new applications*** [for applying to list products that are not already listed on the PL], ***amendment applications*** [for requesting changes to existing PL billing codes], ***expansion applications*** [for separating products listed under one PL billing code into a number of new billing codes] and ***compression applications*** [for consolidating multiple current billing codes with substantially similar products into a single billing code].

Products listed in Part A and Part C are placed in their respective grouping according to the product's functionality, intended use, and available evidence for similarity in clinical outcomes. Each grouping has a set benefit applicable to the medical devices listed in that grouping. The Department manages assessments with assistance from clinicians [Expert Clinical Advisory Groups (ECAGs), and health technology consultants or the Medical Services Advisory Committee (MSAC) where required (e.g. requests for listing of a product with a higher benefit, the product is a new/novel technology, there are no existing Medicare benefits payable, etc).

The MDHTAC [consisting of a range of expert clinician members] and previously the PLAC considered and provided advice on Part A and Part C applications. MDHTAC does not usually consider Part B applications.

For noting, sponsors may also apply to transfer their PL billing codes to another sponsor or delete billing codes. The MDHTAC does not consider these applications as there are no changes to the actual products and no granting decisions are sought for these applications.

Recommendation

I recommend that you s22 GRANT s22 new applications for listing the devices and human tissue products on the PL; s22

Signed and authorised electronically

s22

s22 , Prostheses List Administration Section

17 October 2023

DECISIONS

1. **GRANT** s22 **applications to list new medical devices and human tissue products** recommended as suitable for listing.

☒GRANTED ☐ NOT GRANTED ☐ PLEASE DISCUSS

s22

s22 , Acting Assistant Secretary
Prostheses List Reforms Taskforce
Technology Assessment and Access Division
October 2023

Attachments:

Attachment A: Prescribed List applications with specific issues and questions for consideration
Attachment B: New applications
Attachment D: Amendment and expansion applications

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Application	MDHTAC #1 applications	Cycle	Sponsor	Product Name	Description	Size	ARTG	Category	Sub Category	Group	Sub Group	Suffix	Part	Product Status
s22														
s47G		1/11/2023	Medtronic Australasia Pty Ltd	InterStim X System – Neurostimulator	Recharge-free implantable neurostimulator	One size only	421914	05 - Urogenital	05.07 - Sacral Neuromodulation	05.07.01 - Primary Cell Pulse Generator	Extended Battery Life			Suitable
s22														

s22

s47G

Medtronic Australasia Pty Ltd	InterStim X System – Neurostimulator

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Recharge-free implantable neurostimulator	GSECAG	05 - Urogenital

s22

s22

6.4 - New applications suitable

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