Sacral nerve stimulation for urinary indications

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MSAC application 1115

Assessment report

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared on behalf of the Medical Services Advisory Committee by Ms Amber Watt and, Dr Alun Cameron from the Australian Safety and Efficacy Register of New Interventional Procedures – Surgery (ASERNIP-S) and Mr Richard Norman from the Centre for Health Economics Research Evaluation (CHERE). The report was edited by ASERNIP-S.

Minister for Health and Ageing noted MSAC's advice on

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The procedure

Sacral nerve stimulation (SNS) involves the application of electrical stimulation to the sacral nerve via a totally implantable system. This system consists of an electrode placed extradurally, close to the third sacral anterior root nerve (S3), an implantable pulse generator (IPG) and an extension which connects the electrode to the generator. The procedure is carried out in two phases, allowing for a minimally invasive screening test before proceeding to permanent generator implant if the screening test indicates the viability of the treatment in the individual patient. For the purposes of this review, only the safety and efficacy of chronic SNS (occurring after the placement of an IPG) was assessed.

SNS is proposed for use in adult male and female patients with detrusor overactivity, non-obstructive urinary retention or painful bladder syndrome. All patients eligible for SNS will have experienced one of these conditions for at least 12 months and have failed all appropriate conservative pharmaceutical, behavioural and medical treatments, classifying their urinary dysfunction as refractory to standard treatment.

SNS does not have a direct clinical comparator. Rather, it adds to the existing treatment matrix as a procedure that is more invasive than current clinical management, but far less invasive than the surgical alternatives available to this patient population. Further adding to its 'orphan' status is the fact that SNS is reversible at any point, with the patient able to be returned to conservative treatment or considered for major surgery.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. The MSAC advises the Commonwealth Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. A team from the Australian Safety and Efficacy Register of New Interventional Procedures-Surgical (ASERNIP-S) in South Australia was engaged to conduct a systematic review of the literature on sacral nerve stimulation for urinary indications. An Advisory Panel with expertise in this area then evaluated the evidence and provided advice to MSAC.

This report is an update of MSAC Application 1009: Sacral nerve stimulation for refractory urinary urge incontinence or urinary retention (MSAC 2000). Recent changes to the device (the development of tined leads) and surgical procedure (buttock placement of the generator), along with an increase in the available evidence base for this procedure have resulted in the commissioning of this report.

Additionally, sacral nerve stimulation for faecal incontinence has been evaluated in MSAC Application 1077 (MSAC 2005) and now carries a Medicare rebate, adding further impetus to this evaluation.

MSAC's assessment of sacral nerve stimulation for urinary indications

Clinical need

There was no international literature identified which provided information on the prevalence/incidence of the specific urinary indications suitable for SNS. The manufacturer's estimate cited in the Application and endorsed by Advisory Panel expert opinion indicated that up to 200 Australian patients per year are expected to be candidates for chronic sacral nerve stimulation therapy for urinary indications after the backlog of eligible patients is cleared. The total number of patients treated per year is expected to be limited by the number of specialist surgeons able to undertake this procedure. Expert opinion further indicated that this usage would most likely remain stable or decline slightly over time, as there are no emerging indications for SNS and emerging pharmacological treatment options are providing treatment alternatives.

Safety

Comparative safety data were not available for this procedure, and adverse events were reported inconsistently across the dataset. The safety of chronic SNS for urinary indications was evaluated in a total of 2139 patients, although not all outcomes were reported for every patient.

The SNS procedure was not reported to be associated with any mortality, and the majority of adverse events experienced were of a relatively minor nature. Device removal was reported at a rate of 9.85 per cent across an implanted population of 1361 patients (95% CI: 8.27-11.43).

Approximately 16 per cent of 1444 patients (95% CI: 14.71-18.67) required lead revision or replacement, frequently in order to optimise the clinical effectiveness of the device. Lead migration across the 1561 patients from whom this outcome was reported was 6.98 per cent (95% CI: 5.72-8.24).

The most commonly reported clinical adverse events were pain of undefined location and severity (occurring at a rate of 22.01 per cent across 901 patients; 95% CI: 22.01-25.49), pain specifically at the IPG site (14.0 per cent across 1434 patients; 95% CI: 12.29-15.89) and infection (5.83 per cent across 1303 patients; 95% CI: 4.56-7.10).

A smaller subset of these data reporting safety outcomes on tined leads (867 patients) and buttock placement of the IPG (699 patients) showed lower rates of adverse events with this combination of device and surgical technique, when compared to the older technique of non-tined leads and abdominal generator placement.

Further, the safety of SNS for urinary indications seems generally comparable to that of SNS for the treatment of faecal incontinence.

Effectiveness

Detrusor overactivity

Two randomised controlled trials indicated that SNS was more effective than standard medical management in significantly improving a number of key voiding variables, including reducing the number of voids per day, leakage episodes and severity and degree of urgency. Quality of life outcomes were generally positive with SNS, but remained equivocal overall. Case series data (981 patients) supported the effectiveness of SNS in this patient population, with a maximum follow-up of 60 months.

Non-obstructive urinary retention

One randomised controlled trial comparing SNS to standard medical management showed SNS to be effective in this population. The treatment group displayed significant reductions in all measured catheterisation variables. Evidence from case series data (396 patients) was consistently supportive of the positive treatment effects of SNS. Durability was evaluated up to 70 months, with treatment effectiveness maintained.

Painful bladder syndrome

The limited evidence base available on SNS for this indication (90 patients in six case series) indicated positive treatment effects from SNS in the short-term, but has precluded definitive effectiveness conclusions for this patient population. Further, it was not possible to assess the durability or long-term effects of treatment for this indication, as long-term follow-up data were not available.

Cost-effectiveness

Detrusor overactivity

The Advisory Panel recommended using years of complete dryness as the primary outcome measure as this matches a major clinical trial. It was not possible to construct a generic outcome measure such as a quality-adjusted life year. Of those who underwent peripheral nerve evaluation (PNE), 24.81 per cent were identified as being both suitable for SNS and likely to achieve complete dryness. However, this outcome measure may underestimate the true effect, as those who pass PNE but do not achieve full dryness may experience a significant reduction in incontinence. The cost per additional year of complete dryness was estimated to be $9,866 and this was robust to univariate sensitivity analysis. As there is no benchmark against which this value can be judged, it is not possible to determine whether this ICER represents a good use of scarce societal resources.

Non-obstructive urinary retention

As with detrusor overactivity, the outcome measure was selected to match a major clinical trial. For this indication, a successful result was defined as either catheterisation eliminated or at least a 50 per cent reduction in catheter volume per catheterisation. Of those who undergo PNE, 35.31 per cent are expected to achieve these results (and as before, it is arguable that this underestimates the true benefit). The cost per year over the seven year time horizon of these successful results was estimated to be $7,219. This was robust to sensitivity analysis, although whether this ratio represents good value for money is uncertain.

Painful bladder syndrome

There was no clinical evidence for painful bladder syndrome (PBS) which could be used in an economic evaluation. Therefore, a costing analysis was undertaken. The incremental cost of PNE and SNS was $11,300 per patient.

Financial implication

The expected number of patients to be treated with PNE (of which a proportion will go on to receive SNS) per year is 200, although the likelihood of 200 in the first year is small due to lack of capacity in the field. If these 200 patients were divided equally amongst the three indications considered (detrusor overactivity, urinary retention and painful bladder syndrome) and the conversion rate from PNE to SNS is assumed to be constant across indications, the economic analysis presented here predicts a total net cost of $2.356 million per annum. This consists of costs incurred by the healthcare system (PNE, SNS and dealing with complications), which sum to $2.600 million, minus the cost reduction associated with reduced use of catheters, pads etc. by the individual ($244,000).

However, expert clinical opinion suggests that the division of patients amongst the indications is not likely to be equal; rather it is anticipated that 90 per cent of patients would present with detrusor overactivity and 10 per cent with urinary retention. Should this be the case, the total net cost would be $2.481 million per annum. This consists of costs incurred by the healthcare system (PNE, SNS and dealing with complications), which sum to $2.600 million, minus the cost reduction associated with reduced use of catheters, pads etc. by the individual ($119,000).

Advice

MSAC has considered the safety, effectiveness and cost-effectiveness of sacral nerve stimulation for urinary indications compared with clinical non-surgical management.

MSAC finds there is evidence for the safety of sacral nerve stimulation in adults with detrusor overactivity, non-obstructive urinary retention and painful bladder syndrome refractory to conservative, non-surgical intervention.

MSAC finds sacral nerve stimulation in adults with detrusor overactivity and non-obstructive urinary retention refractory to conservative, non-surgical intervention is more expensive than, but more effective than clinical non-surgical management.

MSAC finds there is insufficient evidence to assess the effectiveness of sacral nerve stimulation in adults with painful bladder syndrome refractory to conservative, non-surgical intervention.

MSAC recognises the social and quality of life issues associated with these conditions.

MSAC advises that public funding should be supported for the procedure of sacral nerve stimulation in adults with detrusor overactivity and non-obstructive urinary retention refractory to conservative, non-surgical intervention.

MSAC advises that public funding should not be supported for the use of sacral nerve stimulation for treatment of patients with painful bladder syndrome.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of sacral nerve stimulation (SNS), which is a therapeutic technology for the treatment of detrusor overactivity, non-obstructive urinary retention and painful bladder syndrome. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including input from clinical experts.

MSAC initially reviewed the evidence associated with SNS for the treatment of urinary indications in June 2000 (MSAC 2000). Due to the relatively high rate of adverse events, uncertainty regarding the long-term effectiveness, and the unfavourable cost-effectiveness ratios associated with the intervention, MSAC recommended that public funding should not be supported for the procedure at that time. An update of the review (Application 1046; no report produced) in May 2002 found that insufficient new evidence had emerged to warrant further consideration of SNS at that time. The current review was sought as a result of the evolution of the SNS device and technique. Further, additional evidence for the procedure has become available since the last report.

Readers are advised that the MSAC recommendation herein is dependent on both the results presented in the current assessment report and those of the previous MSAC report assessing the safety and efficacy of SNS (MSAC 2000). The 2000 MSAC report can be accessed via:
http://www.msac.gov.au/internet/msac/publishing.nsf/Content/MSAC%20Completed%20Assessments%201001%20-%201020

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

An advisory panel with expertise appropriate to this evaluation was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. Membership of the advisory panel is provided at Appendix B.

This report summarises the assessment of current evidence for sacral nerve stimulation for urinary indications.

Background

Sacral nerve stimulation for urinary indications

Urinary indications

Terminology

Where possible, this evaluation will adhere to the standardised terminology for describing lower urinary tract function, as defined by the International Continence Society (Abrams et al 2002) and utilised below.

Detrusor overactivity

Detrusor overactivity is a urodynamic observation characterised by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked. This condition results in a pattern of detrusor overactivity incontinence, within which the lower urinary tract symptoms/symptom syndromes of urge urinary incontinence (UUI) and urgency-frequency (UF) are displayed.

The majority of patients display idiopathic incontinence, where there is no obvious underlying cause; however, detrusor overactivity can be secondary to outlet obstruction, urinary tract infection or neurological abnormalities such as multiple sclerosis.

Typical symptoms of UUI and UF include voiding more than seven times a day, nocturia (voiding twice or more at night), nocturnal enuresis and incontinence without warning (Korda 2004).

Non-obstructive urinary retention

In cases of complete acute retention, the bladder is painful and palpable or percussible, with the patient unable to initiate voiding. Chronic or partial retention is characterised by a non-painful bladder, which remains palpable or percussible after the patient has passed urine. If retention is accompanied by an inability to sense bladder fullness, overflow incontinence may also result.

The potential causes of non-obstructive urinary retention relevant to treatment with SNS include weak or no bladder muscle contraction and pelvic floor dysfunction (Ontario MAS 2005).

Painful bladder syndrome

Painful bladder syndrome (PBS) is the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased day-time and night-time frequency, in the absence of proven urinary infection or other obvious pathology.

The term interstitial cystitis (IC) is often used to refer to this syndrome. However, the International Continence Society notes that interstitial cystitis is a specific diagnosis requiring confirmation by typical cystoscopic and histological features (Abrams et al 2002).

The exact pathology of PBS is unknown, with the condition characterised by the presence of abnormal urinary sensory urgency, frequently accompanied by pain, pressure or spasm. This sensation of urgency results in urinary frequency, with voided volumes being less than normal. Patients may also report bladder pain located suprapubically, vaginally, in the perineum, lower back or medial aspects of the thighs, usually relieved by bladder emptying (Panzera 2007).

Sacral nerve stimulation

Sacral nerve stimulation (SNS) involves the application of electrical stimulation to the sacral nerve via a totally implantable system. This consists of an electrode placed extradurally, close to the third sacral anterior nerve root (S3), an implantable pulse generator (IPG) and an extension which connects the electrode to the generator.

The therapy is based on the observation that electrical stimulation of the sacral nerves can influence bladder, sphincter and pelvic floor behaviour. The mode of action has not been fully elucidated, but is most likely through restoration of the correct balance between excitatory and inhibitory impulses to and from the pelvic organs at a sacral and supra-sacral level (Bemelmans et al 1999). This is supported by recent research utilising positron emission tomography (PET) studies, which indicate that activity in the centres of the brain that control micturition can be enhanced or reduced by SNS, resulting in activation or inhibition of the lower urinary tract (Oerlemans & van Kerrebroeck 2008).

The procedure is carried out in two phases, allowing for a minimally invasive screening test before proceeding to permanent generator implant if the screening test indicates the viability of the treatment in the individual patient.

Phase I – minimally invasive screening test

The minimally invasive screening test is generally performed as an outpatient procedure under local anaesthetic. A needle is inserted into the sacral foramen (generally S3) and the typical nerve responses evaluated. If appropriate responses are demonstrated, electrode lead implantation can proceed in one of two ways, utilising either a temporary lead (one-stage procedure) or tined lead (two-stage procedure).

A temporary lead can be placed into the sacrum via a minimally invasive procedure, and secured to the outside of the patient's sacral area. Small electrical pulses from an external pulse generator are then used to test for a satisfactory response and identify the optimal location for the electrode. The procedure is usually done in the operating theatre under local anaesthetic, with the patient conscious so they can identify where the test stimulation is felt. The procedure can take up to one hour and the patient is usually observed overnight.

The second method for performing the screening test is by implanting a tined lead, which has tines designed to deploy as a fixation system, and is typically placed in the S3 foramen. The lead is then connected via tunnelling to a percutaneous extension, through a small incision made at the prospective neurostimulator site, and then contralaterally exits the skin.

These lead placements are followed by subchronic neurostimulation, which is performed by connecting the electrode lead to an external pulse generator. Over a period of 3 to 7 days, the maximum comfortable level of stimulation is identified and maintained,

alongside a comprehensive record of symptoms and voiding function in order to assess the effectiveness of the stimulation.

Phase II – permanent implantation:

Patients who have demonstrated improvement of at least two major symptoms by greater than 50 per cent on the screening test can be considered for permanent implantation of the sacral nerve pulse generator and electrode.

Initial placement of the IPG was in a subcutaneous pocket in the lower part of the abdominal wall, a procedure requiring a long operating time and three incisions. This procedure frequently resulted in sub-optimal results, with patients reporting displacement or pain at the IPG site post-operatively, and interference from magnetic fields (Scheepens et al 2001).

The current technique involves situating the IPG in a subcutaneous pocket in the lateral-superior quadrant of the buttock, approximately five to ten centimetres caudal to the iliac crest. This allows for a shorter operation and less invasive placement (Scheepens et al 2001).

Stimulation parameters

After placement, stimulation parameters can be adjusted to ensure optimum functioning of the device. Oerlemans and van Kerrebroeck (2008) report that relatively low amplitudes (0-3.0 V) are sufficient and that within the recommended stimulation parameters (210μsec, 10-16 Hz), continuous stimulation is possible without pain sensation.

Unilateral stimulation is the most widely accepted form of SNS, although bilateral stimulation has been proposed to allow lower stimulation intensities, which can assist in lengthening stimulator battery life and reducing the potential for nerve damage.

Intended purpose

Sacral nerve stimulation is proposed for use in adult male and female patients with refractory detrusor overactivity, non-obstructive urinary retention and painful bladder syndrome. All patients eligible for SNS will have experienced one of these conditions for at least 12 months and have failed all appropriate conservative pharmaceutical, behavioural and medical treatments, classifying them refractory to standard treatment.

Further, the eligibility of patients to receive chronic therapeutic SNS will be determined by a documented reduction in symptoms with the minimally invasive screening test, utilising either an implanted tined lead or a temporary peripheral nerve evaluation.

The manufacturer's estimate cited in the Application and endorsed by the Advisory Panel indicated that up to 200 Australian patients per year are expected to be candidates for chronic sacral nerve stimulation therapy for urinary indications. Further, they indicate that the low number of Australian specialist urologists and urogynaecologists with adequate training to perform this procedure would most likely preclude this number of procedures being undertaken in the first few years following funding approval.

Clinical need / burden of disease

Detrusor overactivity

Prevalence estimates of detrusor overactivity resulting in urinary incontinence in the adult population vary considerably for a number of reasons. These include variation in applied definitions, a lack of consensus in measures of severity and significant levels of under-reporting. Further, estimates of the prevalence of incontinence are reported as a whole; detrusor overactivity, stress incontinence and mixed incontinence are not considered separately.

Due to these factors, published Australian prevalence estimates for all forms of incontinence for people living in the community range considerably. Estimates of urinary incontinence among Australian men range from 2.2 per cent to13.0 per cent and Australian women from 19.3 per cent to 37.0 per cent (Australian Institute of Health and Welfare (AIHW) 2006).

Prevalence estimates for urinary incontinence among people living in residential care and institutions are much higher, ranging from 32 per cent to 78 per cent depending on the definition applied (AIHW 2006).

An estimated 117,700 healthy life years were lost in Australia in 2003 due to incontinence (including faecal incontinence), with this burden particularly apparent in those aged over 75 years. The overall burden of incontinence is expected to increase by 110% between 2003 and 2031 (AIHW 2006).

The estimated monetary costs of urinary and faecal incontinence in Australia in the health and residential aged care system in 2003 totalled A$1.5 billion (AIHW 2006). This estimate does not capture the wide range of personal costs associated with incontinence, such as laundry, clothing and time costs. An Australian study by Dowell et al. (1999) in community-dwelling ambulatory women found the median (IQR) total direct cost of urinary incontinence was A$12.89 (A$5.26-22.67) per week, although this cost did not reflect the indirect cost of the time taken to manage incontinence. This cost was significantly correlated with the number and volume of urine leaks. Costs were higher among those aged 65-88 years than any other age group.

Non-obstructive urinary retention

The prevalence of non-obstructive urinary retention and concomitant costs in the Australian population is unclear. Estimates extrapolated from a British study (Evans et al. 2000) suggest that the prevalence of chronic urinary retention ranges from 0.03 per cent to 0.07 per cent in the general population, rising to 0.5 per cent in the population aged over 75 years. Despite this prevalence, little is known about the costs of long-term catheterisation.

Painful bladder syndrome (PBS)

The estimated prevalence of PBS is highly variable, depending on the sensitivity of the survey tool utilised. A 2005 survey undertaken in a population of 1218 women attending a US primary care physician showed that 13 (1.1%) met the criteria for probable IC utilising the O'Leary-Sant index (Rosenberg & Hazzard 2005). However, utilising the Pelvic Pain and Urgency/Frequency patient symptom scale indicated that 154 women

(12.6%) likely had IC. The authors suggest that the true prevalence of IC in women may fall somewhere between these two extremes. Separate data from the US National Institute of Diabetes and Digestive and Kidney Diseases (2007) showed that 94 per cent of adults affected with interstitial cystitis were women. However, due to the diverse symptom constellation, the prevalence of PBS is yet to be adequately quantified.

Existing procedures

The clinical decision-making processes associated with the treatment of detrusor overactivity, non-obstructive retention and interstitial cystitis are presented in Figure 1, Figure 2 and Figure 3.

A broad range of conservative treatment options are available depending on the exact indication. These options include drug therapy with anticholinergics and/or smooth muscle relaxants and behaviour modification techniques such as diet modification, bladder training and pelvic muscle rehabilitation. Interventional therapies such as external and intravesical electrical stimulation may also be considered. However, approximately 40 per cent of patients treated with these therapies either do not achieve an appropriate level of therapeutic benefit, or remain completely refractory to treatment (Oerlemans & van Kerrebroeck 2008). Expert clinical opinion also indicates that the use of botulinum toxin may be trialled in patients with refractory detrusor overactivity or painful bladder syndrome, although in Australia the use of botulinum toxin for these indications is not approved by the Therapeutic Goods Association (TGA), nor publicly funded.

Surgical procedures that may be considered to treat detrusor overactivity include:

- bladder denervation, which involves disrupting the nerves supplying the bladder wall
- augmentation cystoplasty to increase the size of the bladder
- urinary diversion, with or without cystectomy (bladder removal).

Surgical procedures that may be considered to treat non-obstructive retention include:

- permanent indwelling catheter placement
- urinary diversion, with or without cystectomy.

Surgical procedures that may be considered to treat painful bladder syndrome include:

- hydrostatic distension or other bladder instillation therapies
- replacement cystoplasty
- urinary diversion.

Figure 1 **Clinical decision making pathway: sacral nerve stimulation for detrusor overactivity**

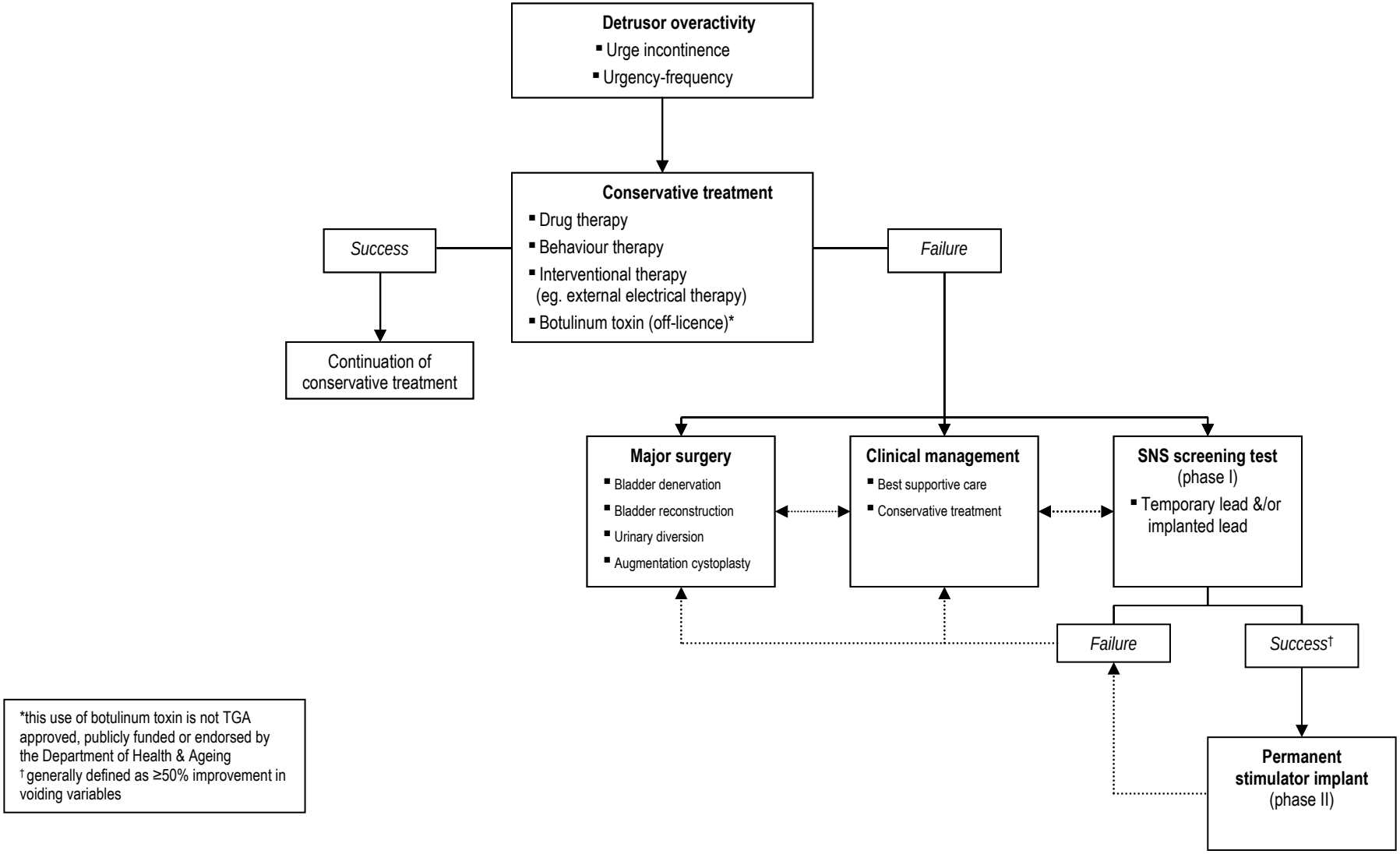


Figure 2 **Clinical decision making pathway: sacral nerve stimulation for non-obstructive urinary retention**

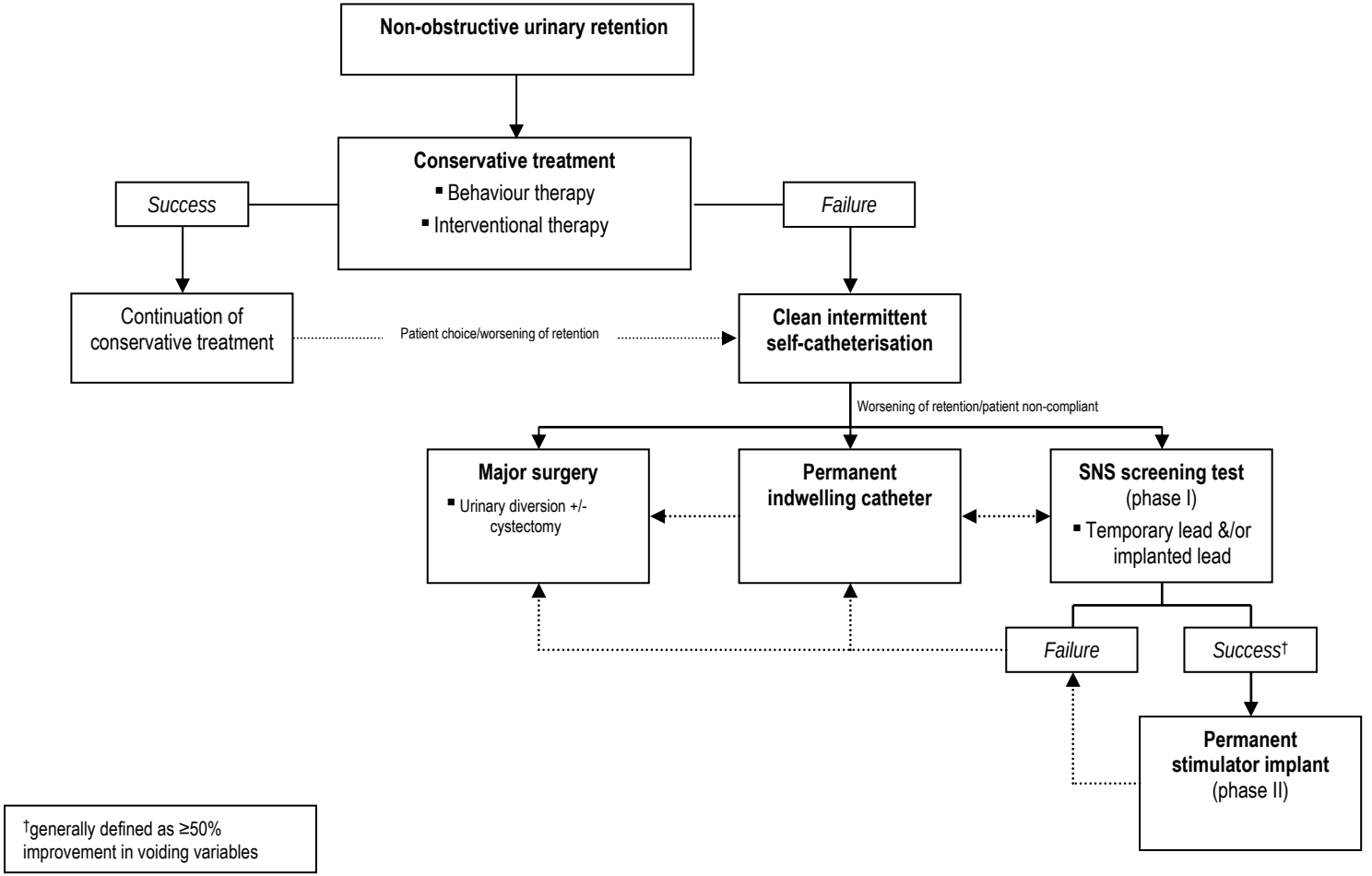
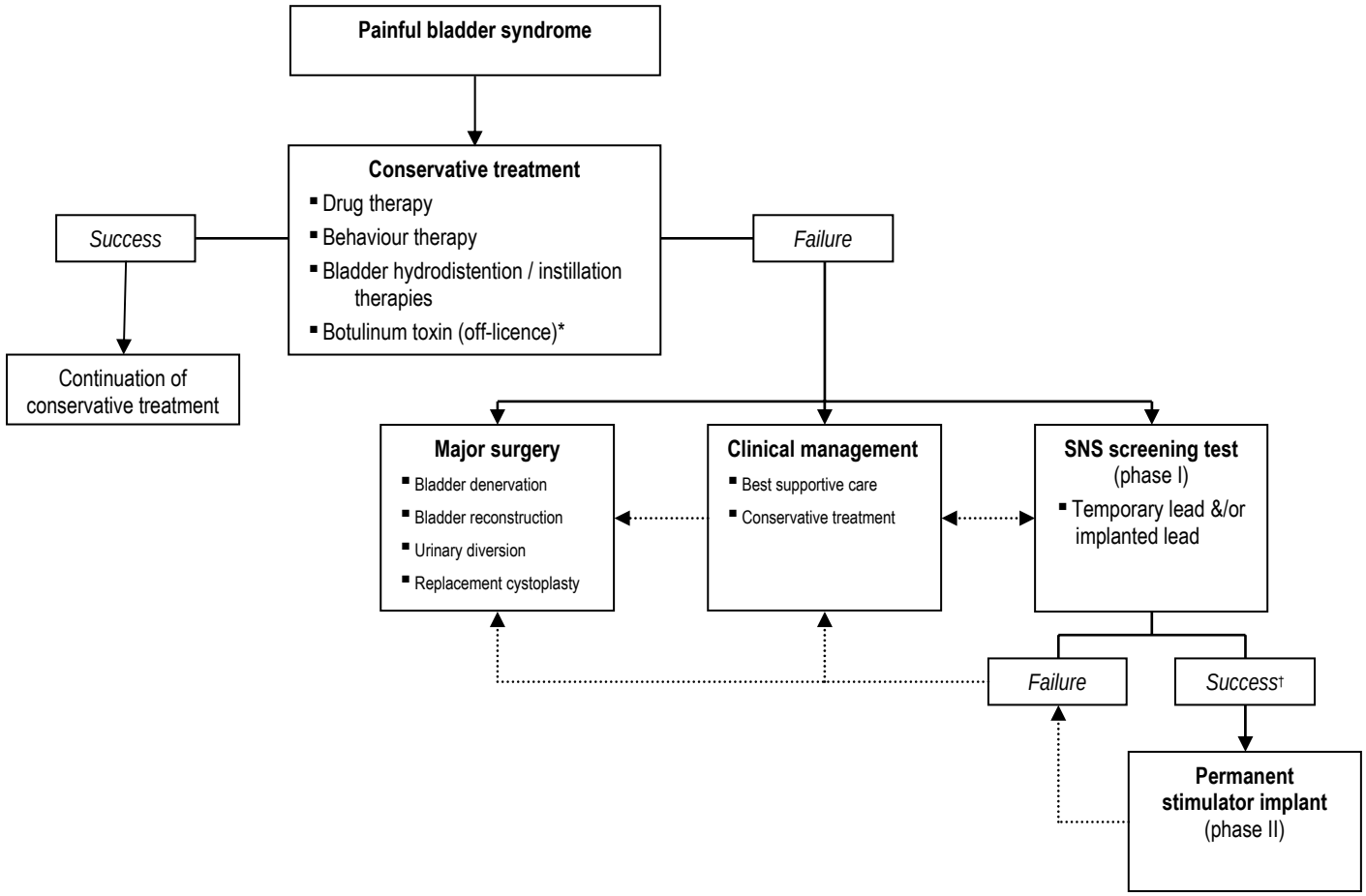


Figure 3 **Clinical decision making pathway: sacral nerve stimulation for painful bladder syndrome**



*this use of botulinum toxin is not TGA approved, publicly funded or endorsed by the Department of Health & Ageing
† generally defined at ≥50% improvement in voiding variables

Comparator

SNS does not have a direct clinical comparator. Rather, it adds to the existing treatment matrix as a procedure that is more invasive than current clinical management, but far less invasive than surgical alternatives. Further adding to its 'orphan' status is the fact that SNS is reversible at any point. Should the device fail or the patient change their mind, the leads and generator can be explanted and the patient returned to conservative treatment or be considered for major surgery.

Marketing status of the technology

The SNS equipment used in the treatment of urinary indications is identical to that used in the treatment of faecal incontinence. The current TGA listings for the SNS device and equipment are listed in Table 1.

Table 1 Items relating to sacral nerve stimulation listed by the TGA

ARTG number	ARTG product number	ARTG label name
125909	209479	Stimulator, electrical, neuromuscular, incontinence, implantable (model number 3023)
96926	167684	Low impedance quadripolar extension kit for spinal cord stimulation
92057	162624	Medtronic Australasia stimulators and accessories, lead introducer kit (various models)
98338	170025	Medtronic Australasia Pty Ltd sacral nerve stimulation lead model 3093 – stimulator, electrical, neuromuscular, incontinence, implantable
33287	Various	Medtronic stimulators and accessories sterile
48654	99275	Medtronic Foramen spinal needles
33200	Various	Medtronic stimulators and accessories

NOTES: TGA Therapeutic Goods Administration; ARTG Australian Register of Therapeutic Goods

Current reimbursement arrangement

The current Medicare Benefits Schedule (MBS) listings for SNS procedures are described in Table 2 and Table 3.

Table 2 Current MBS listing of sacral nerve stimulation: treatment of faecal incontinence

MBS item number	Therapeutic procedure
32213	SACRAL NERVE LEAD(S), placement of, percutaneous using fluoroscopic guidance, or open, and intraoperative test stimulation, for the management of faecal incontinence in a patient who has an anatomically intact but functionally deficient anal sphincter with faecal incontinence refractory to at least 12 months of conservative non-surgical treatment (Anaes.) **Fee:** $596.90 **Benefit:** 75% = $447.70
32214	NEUROSTIMULATOR or RECEIVER, subcutaneous placement of, and placement and connection of extension wire(s) to sacral nerve electrode(s), for the management of faecal incontinence in a patient who has an anatomically intact but functionally deficient anal sphincter with faecal incontinence refractory to at least 12 months of conservative non-surgical treatment, using fluoroscopic guidance (Anaes.) (Assist.) **Fee:** $301.55 **Benefit:** $75% = 226.20

Table 2 continued **Current MBS listing of sacral nerve stimulation: treatment of faecal incontinence**

32215	SACRAL NERVE ELECTRODE(S), management, adjustment, and electronic programming of neurostimulator by a medical practitioner, for the management of faecal incontinence – each day **Fee:** $113.25 **Benefit:** 75% = $84.95; 85% = $96.30
32216	SACRAL NERVE LEAD(S), inserted for the management of faecal incontinence in a patient who has an anatomically intact but functionally deficient anal sphincter with faecal incontinence refractory to at least 12 months of conservative non-surgical treatment, surgical repositioning of, percutaneous using fluoroscopic guidance, or open, to correct displacement or unsatisfactory positioning, and intraoperative test stimulation, not being a service to which item 32213 applies (Anaes.) **Fee:** $536.05 **Benefit:** 75% = $402.05
32217	NEUROSTIMULATOR or RECEIVER, inserted for the management of faecal incontinence in a patient who had an anatomically intact but functionally deficient anal sphincter with faecal incontinence refractory to at least 12 months of conservative non-surgical treatment, removal of (Anaes.) **Fee:** $141.20 **Benefit:** 75% = $105.90
32218	SACRAL NERVE LEAD(S), inserted for the management of faecal incontinence in a patient who had an anatomically intact but functionally deficient anal sphincter with faecal incontinence refractory to at least 12 months of conservative non-surgical treatment, removal of (Anaes.) **Fee:** $141.20 **Benefit:** 75% = $105.90

NOTES: T8.33 SNS contraindicated in all patients under 18 years of age, and in patients 18 years of age or older who: are medically unfit for surgery; are pregnant or planning pregnancy; have irritable bowel syndrome; have congenital anorectal malformations; have active anal abscesses or fistulas; have anorectal organic bowel disease including cancer; have functional effects of previous pelvic irradiation; have congenital or acquired malformations of the sacrum; or have had rectal or anal surgery within the previous 12 months; MBS Medicare Benefits Schedule

Note that the following MBS numbers associated with sacral nerve stimulation for urinary indications relate to the maintenance and replacement of stimulators placed under a different reimbursement arrangement, prior to 30 April 1998. They do not allow for the placement of a new stimulator in a patient without previous SNS treatment.

Table 3 **Current MBS listing for sacral nerve stimulation: treatment of urinary incontinence**

MBS item number	Therapeutic procedure*
36658	SACRAL NERVE STIMULATION for refractory urinary incontinence or urge retention, removal of pulse generator and leads **Fee:** $475.35 **Benefit:** 75% = $356.55 85% = $410.15
36660	SACRAL NERVE STIMULATION for refractory urinary incontinence or urge retention, removal and replacement of pulse generator **Fee:** $230.70 **Benefit:** 75% = $173.05 85% = $196.10
36662	SACRAL NERVE STIMULATION for refractory urinary incontinence or urge retention, removal and replacement of leads **Fee:** $551.10 **Benefit:** 75% = $413.35 85% = $485.90

NOTES: T8.55.1 Items 36658, 36660, and 36662 only apply in the following circumstances: (a) the patient has received a sacral nerve stimulation implant for the management of refractory urinary incontinence or urge retention; (b) the patient requires replacement or removal of the pulse generator and/or leads for the neurostimulator device; and (c) the service referred to in paragraph (a) was rendered to the patient prior to 30 April 1998 and a Medicare benefit was paid for that service under item 30000, 39134, 39139 or 39140; MBS Medicare Benefits Schedule; *refer to 'expert opinion', page 57 for Advisory Panel advice regarding the descriptor terminology utilised.

Approach to assessment

Search strategy

PICO (population, intervention, comparator, outcome) criteria were developed with the assistance of the Advisory Panel to assist in specifying the search strategy (Table 4).

Table 4 PICO criteria

Population[a]	Intervention[b]	Comparator	Outcomes
Patients with refractory detrusor overactivity	Chronic therapeutic sacral nerve stimulation	Standard non-surgical management (best supportive care) Bladder denervation Bladder reconstruction Urinary diversion +/- cystectomy Augmentation cystoplasty	*Effectiveness:* Response rate Voids/day Volume/void Incontinence episodes/day Leakage severity Pad use/day Parameter adjustments Quality of life measures *Safety:* Adverse event rates Revision/explant rates Mortality
Patients with refractory non-obstructive urinary retention	Chronic therapeutic sacral nerve stimulation	Clean intermittent self-catheterisation Indwelling catheter Urinary diversion +/- cystectomy	*Effectiveness:* Response rate Voids/day Volume/void Catheterisations/day Volume/catheterisation Parameter adjustments Quality of life measures *Safety:* Adverse event rates Revision/explant rates Mortality
Patients with refractory painful bladder syndrome	Chronic therapeutic sacral nerve stimulation	Standard non-surgical management (best supportive care) Bladder denervation Bladder reconstruction Urinary diversion +/- cystectomy Augmentation cystoplasty Hydrostatic dilation/ bladder instillation therapies	*Effectiveness:* Response rate Voids/day Volume/void Parameter adjustments Quality of life measures *Safety:* Adverse event rates Revision/explant rates Mortality

[a]All patients eligible for SNS would have suffered from one of these indications for at least 12 months and have failed all other conservative medical, pharmaceutical and behavioural treatments; [b]the eligibility of patients to receive chronic therapeutic SNS would be determined by a reduction in voiding symptoms with the minimally invasive screening test (utilising either an implanted tined lead or a temporary lead for peripheral nerve evaluation).

From expert clinical opinion provided by the Advisory Panel regarding the clinical and technical advances underpinning the evidence base, it was decided to date limit the literature searches from 01 January 2000 onwards in order to identify literature published since the completion of Application 1009. New evidence identified was used in order to

provide a complete evaluation of the current SNS technique, including data arising from the use of tined lead and abdominal placement of the generator where available.

Further, the search strategy utilised in MSAC Application 1077 (MSAC 2005) was updated in order to identify new studies pertaining to the safety of SNS in the treatment of faecal incontinence, as Advisory Panel opinion indicated that the safety data from these studies could be extrapolated to the use of SNS for urinary indications, as the procedure is identical.

Relevant electronic databases were searched for relevant literature up to 15 January 2008. Appendix C details the complete list of bibliographic databases, electronic internet databases and health technology assessment agency websites that were utilised.

The search strategy for this assessment was significantly altered from that utilised in Application 1009. The differences in the search strategies reflect the evolution of the procedure and associated indexing terms. Given the relative recency of the search strategy for Application 1077, this was retained and re-executed in full. The complete search strategies (based on an Ovid platform) are provided in Appendix C, and an overview in Table 5 below.

Table 5 Overview of search terms utilised

Element of clinical question	Keyword search terms
Target population	Detrusor overactivity; urge incontinence; urinary incontinence; overactive bladder; urinary retention; Fowler's syndrome; interstitial cystitis; painful bladder syndrome; chronic pelvic pain
Intervention	Sacral nerve stimulation; sacral anterior root stimulation; SNS; InterStim; peripheral nerve evaluation; neurostimulation; neuromodulation; functional electrical stimulation; FES

Inclusion criteria

Given the scarcity of evidence for the SNS procedure, all clinical studies of chronic sacral nerve stimulation in humans over the age of 18 with non-neurogenic refractory detrusor overactivity, non-obstructive retention or painful bladder syndrome were included. Case reports were not considered for effectiveness outcomes, but were included for the assessment of safety outcomes.

Detailed inclusion and exclusion criteria applied to the identified citations for assessing the safety and effectiveness of SNS are detailed in Appendix C.

Review of literature

Literature databases

Articles were retrieved if they were judged to possibly meet the inclusion criteria. Two reviewers independently applied the inclusion criteria and any differences were resolved by discussion. Excluded studies are listed in Appendix D with reasons for exclusion. The bibliographies of all retrieved publications were hand-searched for any relevant references missed in the database search (pearling).

Data extraction

Data were extracted by one researcher and checked by a second using standardised data extraction tables developed *a priori*. Data were only reported if stated in the text, tables, graphs or figures of the article, or if they could be accurately extrapolated from the data presented. If no data were reported for a particular outcome then no value was tabulated. Descriptive statistics were extracted or calculated for all safety and effectiveness outcomes in the individual studies, including numerator and denominator information.

Description and methodological quality of included studies

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC 2000).

These dimensions (Table 6) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of their determination.

Table 6 Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design.*
Quality	The methods used by investigators to minimise bias within a study design.
Statistical precision	The *P*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

*See Table 7

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 7.

Table 7 Designations of levels of evidence

Level of evidence*	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly-designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

*Modified from NHMRC, 1999.

Included studies were critically appraised for study quality according to the guidelines in Chapter 6 of The Cochrane Reviewers' Handbook (Higgins & Green 2008). Included randomised controlled trials (RCTs) were examined with respect to the adequacy of allocation concealment and blinding (if possible), handling of losses to follow-up, and any other aspect of the study design or execution that may have introduced bias, with reference to the CONSORT Statement (Altman et al 2001). Two reviewers critically appraised each of the included studies, and any differences in interpretation were resolved through discussion. Individual quality scores were not assigned, rather the quality of the included studies was described in a narrative fashion, and any important quality issues highlighted in the discussion of outcomes.

Data analysis

Meta-analysis

Insufficient homogenous RCT data were available to allow meta-analysis to be undertaken.

Handling of non-randomised data

Where statistical pooling was not possible, rates and 95 per cent confidence intervals were calculated from all studies reporting specific outcomes.

Sub-group analyses were carried out for certain variables, with differences in the frequency of pre- and post-treatment outcomes calculated.

Included studies

The studies identified as fulfilling the review inclusion criteria are listed in Appendix E. Those studies which did not meet the inclusion criteria are outlined in Appendix D, along with reasons for their exclusion.

Current and recent clinical trials and health technology assessments of the use of SNS for urinary indications

Websites of clinical trials agencies were searched to identify all relevant ongoing or unpublished clinical trials related to sacral nerve stimulation for urinary indications. These included the Australian New Zealand Clinical Trials Registry, United States National Institute of Health (clinicaltrials.gov) and the National Research Register (UK). As of January 2008, a total of eight trials investigating the use of SNS for urinary indications were identified; these are detailed in Appendix F.

A list of electronic databases and websites of international HTA agencies can be found in Appendix C. As of 12 December 2007, a total of seven health technology assessments, protocols for assessment and reviews were identified; these are presented in Appendix F.

Expert advice

An Advisory Panel with expertise in urology, urogynaecology and consumer issues was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for advisory panels, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the Advisory Panel is provided at Appendix B.

Results of assessment

Descriptive characteristics of included studies

Studies for assessment of safety

Urinary indications

Forty-three studies were identified for inclusion in the assessment of the safety of SNS for urinary indications. This included three studies comparing SNS to standard medical management (Hassouna et al 2000; Jonas et al 2001; Weil et al 2000); one study comparing one-stage implantation to two-stage implantation (Everaert et al 2004); 35 case series and four case reports (see Appendix E). As the control treatment in the comparative studies (standard medical management) does not result in adverse events comparable to those of SNS, the analysis of the SNS arm of randomised comparative studies in isolation resulted in these studies being considered as case series and, as such, any data extracted from them was considered to be Level IV evidence. The 36 descriptive case series were of relatively low methodological quality (Level IV evidence). Sample sizes ranged from six to 235 patients, with safety data reported for a total of 2139 patients overall.

Faecal incontinence

Twenty-four studies were identified for inclusion in the assessment of the safety of SNS for faecal incontinence (see Appendix E). All were descriptive case series (Level IV evidence) of relatively low methodological quality. Sample sizes ranged from four to 100 patients, with safety data reported for a total of 571 patients overall.

Studies for assessment of effectiveness

The systematic literature search revealed a total of four randomised controlled trials that directly compared SNS to standard medical management for the treatment of detrusor overactivity, non-obstructive retention or PBS (Das et al 2004; Hassouna et al 2000; Jonas et al 2001; Weil et al 2000). These studies allowed the assessment of the comparative effectiveness of the procedures within this review. However, the evidence base was diminished by the fact that the studies reported a variety of outcome measures across the range of indications. One comparative study evaluating one-stage versus two-stage implantation was identified (Everaert et al 2004). A subsequent section will examine these studies in greater detail and appraise their methodological quality.

A total of 30 case series assessing the effectiveness of SNS in a variety of populations were identified: 23 reported data specific to the treatment of detrusor overactivity in 26 separate patient groups; 16 reported data relevant to patients with urinary retention; and six reported outcomes for patients with painful bladder syndrome (see Appendix E). A subsequent section will examine these studies in greater detail and briefly appraise their methodological quality.

Across both the comparative studies and the case series, effectiveness outcomes were assessed for a total of 963 patients with detrusor overactivity; 433 patients with non-obstructive urinary retention; and 90 patients with painful bladder syndrome.

Duplication of results

It is highly probable that duplication of results has occurred across this dataset as a number of authors appeared to be involved in multi-centre trials while also reporting single-centre experiences with the device. This was particularly notable in studies originating from The Netherlands and other European centres. However, no study explicitly stated any duplicate reporting of patients, and time periods of the studies were inadequate to definitively determine duplicate reporting, with only three studies able to be excluded due to obvious duplicate reporting (see excluded studies, Appendix D).

Systematic reviews

One systematic review of SNS as a treatment for urinary urge incontinence, published in 2006, was identified (Brazelli et al 2006); this published review appeared to be based on the findings of a National Institute for Clinical Excellence (NICE) health technology assessment.

The systematic review included four randomised controlled trials and 30 case series from a search of the international literature published from 1966-2003. The authors acknowledged the methodological unreliability of the included case series, but found their inclusion necessary. Thus, this systematic review cannot be regarded as Level I evidence. The authors concluded that the evidence indicated that SNS was effective for decreasing symptoms in patients with urge incontinence, however further research was required on the long-term effects and quality of life outcomes.

Critical appraisal of comparative studies

A summary of the quality of the five randomised controlled trials included in this review is reported in Table 8 and Table 9, and briefly outlined below. The criteria used were based on the CONSORT statement of Altman et al (2001).

Study design details

Participants

Explicit inclusion and exclusion criteria for the recruitment of patients were described in three of the five RCT reports (Hassouna et al 2000; Jonas et al 2001; Weil et al 2000). Inclusion criteria generally included being aged over 16 years with urinary symptoms refractory to standard therapy and a normal upper urinary tract with a bladder capacity of greater than 100 mL. Patients were excluded if they had neurological conditions, primary stress incontinence or primary pelvic pain. Weil et al (2000) was the only study to detail an extensive list of exclusion criteria, specifying a number of conditions that would exclude a patient from their study.

The baseline patient characteristics were reported overall for complete study populations by Hassouna et al (2000) and Jonas et al (2001); it was therefore not possible to determine how well matched the demographic and clinical characteristics of the two study groups were at baseline. Other studies reported well-matched groups at baseline.

Randomisation and blinding

Details of methods of randomisation were poorly reported in all studies, with the exception of Weil et al (2000), who reported the use of a computerised random number generator. Blinding was not reported in any study, except by one group of authors (Das et al 2004) who stated that blinding could not be achieved due to the nature of the intervention.

Interventions and outcomes

Interventions were clearly detailed in all studies; primary and secondary outcomes were generally well-defined.

Results reporting and analyses

Numbers analysed and statistical methods

Analysis techniques were not consistently reported. Further, while the statistical tests employed were generally well-described, the significance levels were infrequently reported and not stated to be pre-defined. Ancillary analyses were undertaken in a number of studies.

Outcomes and estimation

The results for each primary outcome defined were reported in each study, and all studies included some measure of estimation, including the use of standard deviations, confidence intervals and quartile ranges as appropriate.

Adverse events were not well reported. No study reported on adverse events in the control arms of the studies, and only two studies reported absolute numbers of adverse events in the SNS arms (Weil et al 2000; Everaert 2004).

Follow-up and losses to follow-up

Maximum follow-up amongst the five randomised controlled trials ranged from 6 months to 36 months, as shown in Table 9. As a number of the studies employed a crossover design, allowing patients in the control group to cross over to the treatment group after six months if still medically indicated, there is little comparative effectiveness evidence available beyond six months.

Only two of the studies reported losses to follow-up (Weil et al 2000; Everaert et al 2004), with only Evereart et al (2004) detailing reasons for these losses. The design of the studies, with multiple time-points for outcome assessment and patient crossover, made it impossible to evaluate the flow of the patient cohorts through the study arms; hence, losses to follow-up could not be evaluated by external data review.

Table 8 Critical appraisal summary of comparative studies: study design details

Study NHMRC level*	Sample size	Indication/s			Participants	Randomisation details	Blinding	Interventions and outcomes
		DO	UR	PBS				
Chronic SNS vs. standard conservative medical management								
Hassouna 2000 *Level II*	Total: 51 SNS: 25 SMM: 26	✓			Eligibility criteria defined (cohort part of larger multi-centre trial) Comparability of baseline characteristics of groups not reported or evaluated	…	…	Interventions detailed Primary & secondary outcomes defined
Jonas 2001 *Level II*	Total: 68 SNS: 37 SMM: 31		✓		Eligibility criteria defined (cohort part of larger multi-centre trial) Comparability of baseline characteristics of groups not reported or evaluated	…	…	Interventions detailed Primary & secondary outcomes defined
Weil 2000 *Level II*	SNS: 20 SMM: 23 SNS (after crossover): 42	✓			Eligibility criteria defined Groups well matched for all outcome measures & patient attributes at baseline	1:1 target ratio Computerised random number generator	…	Interventions detailed Outcomes defined
one-stage implantation vs. two-stage implantation								
Everaert 2004 *Level II*	Total: 42 1-stage: 21 2-stage: 21	✓	✓		Eligibility criteria defined Groups well matched at baseline	Patients 'randomised according to their symptoms…and age' No details of concealment or implementation	…	Interventions detailed Primary outcomes & end-points defined
Chronic SNS vs. standard conservative medical management – QoL outcomes only								
Das 2004 *Level II*	Total: 89 SNS: 56 SMM: 33	✓	✓		Eligibility criteria not defined Groups well matched for depression levels at baseline; other attributes not reported	No details of randomisation, concealment or implementation	Investigators state that blinding could not be achieved due to the nature of the intervention	Interventions detailed Outcomes based on patient responses to validated QoL questionnaires

NOTES: *NHMRC Hierarchy of Evidence (2000); … not reported; QoL quality of life; SNS sacral nerve stimulation; SMM standard medical management; DO detrusor overactivity; UR urinary retention; PBS painful bladder syndrome

Table 9 Critical appraisal summary of comparative studies: results details

Study	Numbers analysed	Statistical methods	Outcomes and estimation	Ancillary analyses	Adverse events	Follow-up
Chronic SNS vs. standard conservative medical management						
Hassouna 2000	Interim analysis performed (cohort part of larger multi-centre trial)	Sequential data analysis Significance levels stated & adjusted for some variables	Results for each outcome detailed Standard deviations reported	Stimulation on vs. stimulation off in IPG-implanted patients	Probability of adverse events in larger population reported Absolute numbers of events not reported	6-24 months Losses: …
Jonas 2001	Intention-to-treat or per-protocol analysis not defined	Tests described Significance levels not stated	Results for each outcome detailed Standard deviations reported	Stimulation on vs. stimulation off in IPG-implanted patients	Probability of adverse events in larger population reported Absolute numbers of events not reported	SNS: 18 months SMM: 6 months Losses: …
Weil 2000	Treatment algorithm presented – analysis of initial SNS & crossover patients	Tests well described Significance levels stated	Results for each outcome detailed 95% CI reported	Stimulation on vs. stimulation off in IPG-implanted patients	Absolute numbers of events recorded for IPG-implanted patients No events reported for SMM	Median: 18 (6-36) months Losses: 4/42 (reasons not detailed)
one-stage implantation vs. two-stage implantation						
Everaert 2004	Intention-to-treat analysis performed	Tests described Significance levels not stated	Results for each outcome detailed Standard deviations/quartile ranges reported as appropriate	Sub-group analysis performed for patients with DO compared to patients with UR	Absolute numbers of events recorded for both groups	Up to 24 months Losses: 2/42 (1 death not attributable to SNS & 1 explant due to infection with chemotherapy)
Chronic SNS vs. standard conservative medical management – QoL outcomes only						
Das 2004	Intention-to-treat or per-protocol analyses not defined	Tests described Significance levels stated	Results for each outcome detailed Standard deviations reported	No sub-group analyses performed	…	Up to 12 months for SNS Up to 6 months for SMM Losses: …

NOTES: … not reported; QoL quality of life; SNS sacral nerve stimulation; SMM standard medical management; DO detrusor overactivity; UR urinary retention; PBS painful bladder syndrome

Critical appraisal of case series

An appraisal of the quality of the 30 case series included in this review for effectiveness is reported in Appendix G, and briefly summarised below.

Study design details

Participants

Sample sizes across the studies ranged from six to 196 patients. The allocation of these patients to SNS was rarely performed in a consecutive manner, and the majority of studies reported undertaking retrospective, rather than prospective, recruitment and analysis.

Interventions and outcomes

Interventions were generally clearly detailed; primary and secondary outcomes were well-defined overall. The majority of studies reported objective voiding data, augmented by subjective patient responses using a variety of validated and non-validated scales.

Results reporting and analyses

Statistical methods

The analysis techniques employed were not consistently reported. Further, while the statistical tests employed were generally well-described for pre- and post-IPG implantation analyses, the significance levels were infrequently reported and not explicitly stated to be pre-defined.

Follow-up and losses to follow-up

A wide range of follow-up times were reported. While the majority of outcomes reported were to specific time points, it was difficult to assess the final duration of follow-up; analysis of durability outcomes was precluded by this lack of data.

Large losses to follow-up were reported by several studies, particularly those that examined patient cohorts retrospectively. The reasons for these losses were rarely reported, which portends the possibly of attrition bias in the reported data.

Is it safe?

Forty-three studies were identified that reported safety data on a total of 2139 patients treated with chronic SNS for urinary indications. These data were augmented with those from a further 24 studies reporting safety data on chronic SNS for the treatment of faecal incontinence in a total of 571 patients. Only chronic sacral nerve stimulation was considered; the safety of PNE (or stage one testing of the two-stage procedure) was not evaluated.

The safety of SNS was evaluated for pooled groups across the evidence base, as expert clinical advice indicated that data pooling was justified based on the identical nature of the device and procedure used for all indications. Additionally, in most studies the safety profile of SNS was based on pooling data from all patients under investigation. Safety outcomes were evaluated for all indications overall and further considered separately by indication (faecal or urinary incontinence), lead type (tined or non-tined) and location of generator (abdominal or buttock), where clinically relevant and adequate data available.

There were no appropriate comparative data available, as the most frequently utilised comparator, standard medical management, is a relatively low-risk approach. Thus, there were no safety data reported for the comparator in any study, precluding any comparison between the two treatment modalities. Safety data from the SNS arms of comparative studies have been included in the overall safety evaluation.

The adverse events are considered in three categories: technical events directly related to the SNS device and its components; clinical events related to the procedure; and explantation. The explant rate is presented separately as permanent removal of the leads and generator may be performed for either technical or clinical reasons.

Adverse events were reported inconsistently across the dataset, with no standardised definitions utilised. As a result, the incidence of some adverse events is highly variable between studies, and may be representative of clinically distinct groups that are inadequately described in the primary literature or changes to the focus of outcomes reporting as the technique has become more sophisticated.

Adverse events by indication

All indications

Three studies stated that there were no complications after neuromodulator implant in a total of 39 patients (Roupret et al 2004; Jarrett et al 2005a; Michelsen et al 2006). However, these studies did not specify what was considered an adverse event; hence these patients were not included in the totals reported.

Additionally, there were three studies that reported on the probability of adverse events at 12 months post-implantation, rather than reporting the actual rate of occurrence (Hassouna et al 2000; Jonas et al 2001; Seigel et al 2000). Further, the method underpinning the calculation of these data was not explicitly defined. Therefore, these data could not be incorporated into the calculations of adverse events and are reported separately in Table 10. Both the sample sizes and the percentage probability of adverse events were the same across all three studies, indicating that this probabilistic modelling was based on the same cohort of 281 patients and was reported in duplicate.

Table 10 Probability of adverse events at 12 months post-implantation

Adverse event	Probability of occurrence at 12 months (%)
Technical adverse events	
Technical problems	1.7
Suspected device problems	1.6
Suspected lead migration	8.4
Infection	6.1
Transient electric shock	5.5
Device rejection	0.5
Revision surgery	33.0
Clinical adverse events	
Pain at IPG site	15.3
New pain	9.0
Pain at lead site	5.4
Adverse change in bowel function	3.0
Change in menstrual cycle	1.0
Adverse change in voiding function	0.6
Persistent skin irritation	0.5
Suspected nerve injury	0.5
Other	9.5

NOTES: IPG implantable pulse generator

Table 11 details the collective reported adverse events in all patient groups treated with SNS for primary faecal incontinence or urinary indications (including detrusor overactivity, non-obstructive retention and painful bladder syndrome), with rates and 95 per cent confidence intervals calculated to aid in comparison and interpretation of the data.

Table 11 Adverse events summary: all indications

Outcome	Number of studies	Patients N=	Incidence n=	Rate (%)	95% confidence intervals
Technical adverse events					
Lead/electrode migration	37	1920	140	7.29	6.13-8.45
Generator malfunction	12	610	23	3.77	-
Lead replacement/repositioning	40	1776	293	16.50	14.77-18.23
Clinical adverse events					
Pain at IPG site	33	1632	233	14.28	12.58-15.98
Other pain	22	1097	218	19.87	17.51-22.23
Infection	37	1670	94	5.63	4.52-6.74
Seroma/haematoma	17	794	31	3.90	-
Wound complications	10	575	20	3.48	-
Other	20	1120	245	21.88	19.46-24.30
Device explant					
Permanent explant	34	1593	161	10.11	8.63-11.59

NOTES: 95% confidence intervals not calculated if rate <5%; IPG implantable pulse generator

Technical adverse events

While lead migration was reported across a relatively large sample of patients, it was not possible to evaluate the durability of lead placement, as leads were reported to migrate at time points ranging from immediately to 60 months post-implantation. Additionally, actual rates of migration may be higher than indicated, as not all studies reported the use

of x-ray or other diagnostic methods to confirm lead migration before replacement or attempted repositioning.

Generator malfunction was attributed to battery depletion in seven cases, with one study reporting a battery life of 5.3 years (Kessler et al 2007) and another, 7.31 years (Datta et al 2008). Other potential reasons for malfunction were not explicitly documented.

The need for lead replacement or repositioning was the most frequently reported technical adverse event, with leads frequently being replaced or repositioned in an attempt to optimise the clinical effectiveness of the SNS. Studies did not necessarily require definitive evidence of lead migration before attempting repositioning or replacement – the surrogate outcome of loss of efficacy was generally considered adequate to justify lead replacement or repositioning. This may account for the discrepancy between the rates of lead migration and replacement/repositioning.

Clinical adverse events

The outcome of 'other pain' refers to new pain reported after the SNS procedure in areas not directly related to the surgical component of the procedure or the SNS device specifically. Pain was reported in a number of areas, including the legs, perineum and genitalia, with severity ranging from transient to intractable.

Infection was generally reported as superficial (resolved with antibiotics). Only three studies reported deep infections that necessitated device removal (7/142 patients; Aboseif et al 2002; Latini et al 2006; Washington et al 2007). Additionally, three herpes flares (Sutherland et al 2007) and five urinary tract infections (Starkman et al 2007) were reported, but not included in the infection total as they most likely represented the exacerbation of pre-existing conditions.

The most commonly reported 'other' adverse event relating to SNS (in patients initially diagnosed with urinary incontinence) was bowel disturbance, specifically reported in 31 patients across seven studies (DasGupta et al 2004; Edlund et al 2000; Hedlund et al 2002; Janknegt et al 2001; Sutherland et al 2007; van Voskuilen 2006; Weil 2000). There were also some current-related problems reported, with some patients reporting minor localised electric shocks or interference from other electrical fields. Damage to the generator after falls, magnetic resonance imaging and massive weight loss was also reported.

Device explant

Studies did not consistently report specific reasons for explanting the device from individual patients. Generally reported reasons for device removal included loss of efficacy, infection, intractable pain and patient choice.

Mortality

Only four studies reported on mortality in their patient cohort (Datta et al 2008; Everaert 2004; Faucheron et al 2004; Groenendijk et al 2007). Of the two deaths in 164 patients, neither was considered attributable to SNS.

Urinary indications

Table 12 details the collective reported adverse events in patients receiving chronic SNS for urinary indications only (including detrusor overactivity, non-obstructive retention and painful bladder syndrome).

Table 12 Adverse events with SNS for urinary indications

Outcome	Number of studies	Patients N=	Incidence n=	Rate (%)	95% confidence intervals
Technical adverse events					
Lead/electrode migration	23	1561	109	6.98	5.72-8.24
Generator malfunction	10	569	21	3.69	-
Lead replacement/repositioning	26	1444	241	16.69	14.71-18.67
Clinical adverse events					
Pain at IPG site	23	1434	202	14.0	12.29-15.89
Other pain	15	901	205	22.75	22.01-25.49
Infection	24	1303	76	5.83	4.56-7.10
Seroma/haematoma	11	621	18	2.90	-
Wound complications	8	557	18	3.23	-
Other	18	1076	242	22.49	20.0-24.98
Device explant					
Permanent explant	22	1361	134	9.85	8.27-11.43

NOTES: 95% confidence intervals not calculated if rate <5%; IPG implantable pulse generator

In one transverse cohort study (van Voskuilen et al 2006), the authors examined trends in the number of adverse events and re-operations during the study period in patients treated with SNS for urinary indications. In the patients implanted before 1995, the mean number of re-operations required was 1.56, while in patients implanted after 1995, the mean requirement for re-operations decreased to 0.49 (P<0.0001). This outcome measure demonstrated an increase in the safety of SNS over time.

Faecal incontinence

Table 13 details the collective reported adverse events in patients receiving chronic SNS for the treatment of faecal incontinence.

Table 13 Adverse events with SNS for faecal incontinence

Outcome	Number of studies	Patients N=	Incidence n=	Rate (%)	95% confidence intervals
Technical adverse events					
Lead/electrode migration	14	359	31	8.64	5.73-11.55
Generator malfunction	2	41	2	4.88	-
Lead replacement/repositioning	14	332	52	15.66	11.75-19.57
Clinical adverse events					
Pain at IPG site	10	198	13	6.57	3.12-10.02
Other pain	7	196	19	9.69	5.55-13.83
Infection	13	367	18	4.90	2.69-7.11
Seroma/haematoma	6	173	13	7.51	3.58-11.44
Wound complications	2	18	2	11.10	-1.78-23.98
Other	2	44	3	6.82	0.43-13.21
Device explant					
Permanent explant	12	232	27	11.64	7.51-15.77

NOTES: 95% confidence intervals not calculated if rate <5%; IPG implantable pulse generator

There are some differences evident in the rates of various adverse events between the indications, for which there may be a number of explanations. It is possible that the increased rates of lead migration and generator malfunction in the patients with faecal incontinence reflects the slight dominance of marginally older studies utilising older technology.

Further, the higher rate of lead replacement/repositioning in the studies of urinary incontinence may indicate that clinicians are increasingly prepared to reposition or replace leads in an attempt to obtain maximum clinical efficacy from the device.

Generally higher rates of clinical complications in patients treated for urinary indications may reflect the accumulating body of evidence over time and resultant changes to the emphasis of outcomes reporting, rather than genuine clinical differences.

Adverse events by lead type

The potential for differing safety profiles between tined and non-tined leads for both urinary indications and faecal incontinence is considered in Table 14. These data, separated by indication, are presented in Appendix H. Overall, data on 867 patients with tined leads have been compared with data on 557 patients with non-tined leads, although not all outcomes have been reported for every patient.

Table 14 Adverse events with the use of tined and non-tined leads for all indications

Indication	Leads	Number of studies	Patients N=	Incidence n=	Rate (%)	95% confidence intervals
Technical adverse events						
Lead/electrode migration	Tined	9	560	15	2.68	-
	Non-tined	10	243	37	15.23	10.71-19.75
Generator malfunction	Tined	2	94	2	2.13	-
	Non-tined	2	45	4	8.89	1.76-16.02
Lead replacement/repositioning	Tined	7	415	30	7.23	4.74-9.72
	Non-tined	14	291	108	37.11	31.56-42.66
Clinical adverse events						
Pain at IPG site	Tined	7	371	14	3.77	-
	Non-tined	12	302	68	22.51	17.80-27.22
Other pain	Tined	3	97	15	15.46	8.27-22.65
	Non-tined	6	207	38	18.36	13.09-23.63
Infection	Tined	8	386	26	6.74	4.24-9.24
	Non-tined	9	272	11	4.04	-
Seroma/haematoma	Tined	3	127	5	4.72	-
	Non-tined	5	93	6	6.45	1.46-11.44
Wound complications	Tined	2	95	3	3.16	-
	Non-tined	4	90	7	7.78	2.25-13.31
Other	Tined	3	83	4	4.82	-
	Non-tined	5	131	29	22.14	15.03-29.25
Device explant						
Permanent explant	Tined	7	346	37	10.69	7.43-13.95
	Non-tined	9	183	28	15.30	10.08-20.52

NOTES: 95% confidence intervals not calculated if rate <5%; IPG implantable pulse generator

From this limited dataset, it appears that there is an increased occurrence of lead migration and generator malfunction, and a substantially increased need for lead

replacement/repositioning when non-tined leads are utilised. There also appears to be a relationship between increased levels of pain at the IPG site and the use of non-tined leads. However, this may be attributable to the concomitant use of non-tined leads and abdominal IPG placement.

There is also a notably higher rate of device explant with non-tined leads, suggesting the occurrence of more complex adverse events necessitating device removal when these leads are used.

Data reported by Sutherland et al (2007) supports the suggestion that tined leads are safer than non-tined leads. While the authors did not report all safety outcomes by the lead type in their population of 104 patients, it was stated that tined leads had an overall lower adverse event rate compared to non-tined leads (28 per cent and 73 per cent respectively).

Adverse events by generator location

The potential for differing safety profiles between abdominal and buttock placement of the generator for all indications is considered in Table 15. These data, separated by indication, are presented in Appendix H. Overall, data on 699 patients with buttock-placed generators have been compared with data on 319 patients with abdominally-placed generators, although not all outcomes have been reported for every patient.

Table 15 Adverse events with different generator locations: all indications

Indication	Leads	Number of studies	Patients N=	Incidence n=	Rate (%)	95% confidence intervals
Technical adverse events						
Lead/electrode migration	Buttock	8	392	14	3.57	-
	Abdomen	4	109	12	11.00	5.13-16.87
Generator malfunction	Buttock	2	46	1	2.17	-
	Abdomen	2	62	6	9.67	2.31-17.03
Lead replacement/repositioning	Buttock	11	449	43	9.58	6.86-12.30
	Abdomen	5	115	28	24.35	16.51-32.19
Clinical adverse events						
Pain at IPG site	Buttock	10	237	21	8.86	5.24-12.48
	Abdomen	5	122	37	30.32	22.16-38.48
Other pain	Buttock	5	155	29	18.71	12.57-24.85
	Abdomen	3	101	18	17.82	10.36-25.28
Infection	Buttock	11	235	15	6.38	3.26-9.50
	Abdomen	1	53	1	1.89	-
Seroma/haematoma	Buttock	5	134	4	2.99	-
	Abdomen	1	16	1	6.25	-4.36-18.11
Wound complications	Buttock	1	30	2	6.67	-1.07-14.41
	Abdomen	1	42	1	2.38	-
Other	Buttock	4	95	6	6.32	1.43-11.21
	Abdomen	3	104	28	26.92	18.40-35.44
Device explant						
Permanent explant	Buttock	9	230	23	10.00	6.12-13.88
	Abdomen	2	48	3	6.25	0.39-12.11

NOTES: 95% confidence intervals not calculated if rate <5%; IPG implantable pulse generator

Key results from this comparison indicate that buttock placement of the IPG is less likely to be complicated by pain at the IPG site than abdominal placement. A smaller patient sample also suggests a lower incidence of generator malfunction amongst buttock-placed generators.

While this relatively limited dataset appears to suggest overall that buttock placement is less likely to result in adverse events than abdominal placement, these findings should be interpreted with care due to the co-evolution of the SNS device and surgical technique. A number of the studies utilising buttock placement of the IPG were also reported that tined leads were used, while the majority of studies utilising abdominal placement of the IPG reported this in conjunction with non-tined leads. This confounding of the data has prevented definitive conclusions regarding any association between IPG location and complication rates from being drawn.

Other safety considerations

While the following patients do not form part of the safety populations described above, the complex circumstances surrounding the application of SNS in these sub-populations may warrant consideration.

SNS in patients with cardiac pacemakers

One study described a population of three patients with existing cardiac pacemakers who were implanted with InterStim generators after successful test stimulation for the treatment of refractory urgency, frequency and urge incontinence (Wallace et al 2007).

All patients experienced reduction in key voiding variables after implantation without any adverse events or interference with cardiac pacing, even at maximal stimulation (investigated by cardiac interrogation of the pacemakers). With a maximum of 24 months follow-up, all patients were subjectively satisfied with their SNS devices and were without any cardiac events, specifically palpitations, light-headedness or new cardiac symptoms.

SNS and pregnancy

Currently, sacral nerve stimulation is not recommended during pregnancy due to unresolved concerns surrounding potential teratogenic effects of neuromodulation, the possibility of adverse events following stimulation deactivation and implant damage/displacement during vaginal delivery that may compromise future functioning of the device.

One study examined the course of treatment for six women who planned or unexpectedly achieved pregnancy while receiving chronic SNS (Wiseman et al 2002). In five patients, the stimulator was deactivated between weeks 3 and 9 of gestation and in one patient, stimulation was ceased 2 weeks before conception. Three patients had normal vaginal delivery and three patients had caesarean deliveries. All neonates were healthy.

In two patients, SNS was no longer required after delivery, and the devices were not reactivated. Two patients achieved good urinary function with the reactivation of stimulation, one maintained a poor level of function (comparable to prior to pregnancy), and one patient lost treatment effect after vaginal delivery.

Summary of safety outcomes

- This assessment of the safety of chronic sacral nerve stimulation was limited by the absence of comparative data. Safety was evaluated in a total of 2139 patients with urinary indications and 571 patients with faecal incontinence.

- No mortality associated with the SNS device or procedure was reported.

- The need for lead replacement/repositioning was the most frequently reported technical adverse event (16.5 per cent across 1776 patients; 95% CI: 14.77-18.23); pain of unspecified location and severity was the most frequently reported clinical adverse event (19.78 per cent across 1097 patients; 95% CI: 17.51-22.23).

- There was an overall explant rate of 10.11 per cent (95% CI: 8.63-11.59) across the complete dataset for a variety of technical and clinical reasons.

- The examination of the safety of tined compared to non-tined leads and abdominal compared to buttock placement of the generator was confounded by their simultaneous evolution. However, the current combination of tined leads and a buttock-placed generator appears to result in lower rates of adverse events than previous combinations of leads and placement sites.

- Considered separately, the safety of SNS for urinary indications appears generally comparable to that of SNS for faecal incontinence.

From the limited case series data available, it appears that the SNS procedure is safe and associated with few major complications, although minor lead revision surgery may be required by approximately 16 per cent of the implanted population to ensure optimal clinical effectiveness.

Is it effective?

Detrusor overactivity

Voiding outcomes

Comparative studies

Two studies were identified that compared chronic sacral nerve stimulation with continued conservative treatment in the treatment of detrusor overactivity (Hassouna et al 2000; Weil et al 2000). Both studies employed a crossover design, allowing eligible patients randomised to the control arm to receive an IPG after six months if it remained clinically indicated. Although both studies reported outcomes at six months follow-up, the outcome measures differed between the two studies.

At six months, Hassouna et al (2000) reported statistically significant improvements in mean voids per day (9.3±5.1 vs 15.7±7.6, P <0.0001), mean volume per void (226±124mL vs 123±75mL, P =0.001) and degree of urgency (P =0.01) in the SNS group of 25 patients compared to the control group of 26 patients.

Further, a greater proportion of patients receiving SNS demonstrated a 50 per cent or greater decrease in voids and/or a return to a normal voiding pattern of four to seven voids per day than that demonstrated by the control group at 6 months follow-up (Table 16). However, the statistical significance of these differences was not reported.

Table 16 Voiding outcomes at six months (Hassouna et al 2000)

	≥50% decrease &/or 4-7 voids/day	<50% decrease in voids/day	No reduction in voids/day	Device explanted
SNS	14/25 (56%)	8/25 (32%)	2/25 (8%)	1/25 (4%)
Control	1/26 (4%)	8/26 (32%)	17/26 (64%)	0
P value	…	…	…	…

NOTES: … not reported

Changes in outcome measurements from baseline to six months and between treatment and control groups were examined by Weil et al (2000). When comparing baseline to six month measurements in the SNS group, statistically significant improvements were found in mean leakage episodes and mean pad use (P <0.0005). This represents a decrease in leakage episodes, from a mean of 13.5 per day (95% CI: 10.3-16.7) pre-SNS to a mean of 1.4 per day (95% CI: 0-3.2) at 6 months post-implantation. Clinically, pad use decreased from a mean use of 8.7 per day (95% CI: 5.8-11.6) to 0.7 per day (95% CI: 0-1.3). A non-significant decrease in mean leakage severity was also reported. No significant changes from baseline were evident for these outcomes in the control group.

There were significant differences found in favour of the SNS group over the control group, with reductions in leakage episodes (P <0.0005), mean leakage severity (P =0.047) and pad usage (P <0.0005). Fifty-six per cent (9/16) of SNS patients who could be evaluated reported complete dryness at six months as compared to 4.5 per cent (1/22) of control patients. Seventy-five and 85 per cent of SNS patients had at least 90 per cent improvement in leakage and reduction in pad usage, respectively; no control patient achieved these levels of improvement.

Both studies evaluated the dependency of treatment effects on active stimulation by temporarily discontinuing and then resuming stimulation in successfully treated SNS

patients. Rebound effects were observed upon the cessation of stimulation, with patients returning to baseline voiding status. Outcome measures significantly improved again with the resumption of stimulation.

Case series

Due to the small number of comparative studies available, effectiveness outcomes from Level IV studies (case series) were also included for assessment.

The effect of SNS on voiding variables was reported for a total of 26 patient groups. These groups ranged in size from five to 96 patients, with a median sample size of 29 patients. Complete data on voiding variables for these studies are reported in Appendix I.

Response rates were reported for 14 of the 26 patient groups, based on widely variable definitions including: completely dry; ≥50 per cent improvement in presenting symptoms; or subjective patient responses of 'good effect' or 'insufficient effect'.

Considering the response rate as a generic measure, the rate of positive response to SNS ranged from 17 per cent (complete dryness at six months in 1/6 patients; Roupret et al 2004) to 100 per cent (≥50 per cent improvement in presenting symptoms for 12/12 patients; Amundsen et al 2002). The median response rate across all definitions for the 14 patient groups was 80 per cent.

Incontinent episodes per day were reported for 17 of the 26 patient groups, with a decrease in the total number of incontinent episodes reported for all 17 groups. There was a statistically significant decrease in incontinent episodes between the baseline and follow-up measures in 12 of the 15 patient groups for whom significance testing was undertaken.

The severity of this leakage was evaluated in eight of the 26 patient groups. There were three different methods of assessing leakage severity: patient report of 'heavy' leaking episodes; patient ranking of incontinence severity on a scale; or an objective measurement of grams of leakage. Regardless of the measurement method used, the severity of leakage was found to be decreased in all of the eight studies reporting this variable. Five studies further reported the significance of this finding, with statistically significant decreases in leakage severity reported for four of the five patient groups.

Reduction in incontinence was further evaluated in 15 patient groups by the reporting of pad/diaper use per day. The number of pads used decreased in all groups. All tested for the significance of this decrease, with 12 of the 15 groups achieving a decrease of statistical significance for this variable.

The number of voids per day was reported for 15 of the 26 patient groups. A decreased number of voids per day were reported by every study (15/15). Eleven of the 15 studies reported undertaking some form of significance testing for this variable; nine of the 11 reported this decrease in voids per day to be statistically significant ($P < 0.05$).

Volume per void was reported for 10 of the 26 patient groups. An increased volume of urine per void was reported by all 10 studies. Six of the 10 studies undertook significance testing; the increased volume was reported as statistically significant by all six ($P < 0.004$).

The maximum voided volume was reported for only two of the 26 patient groups. A statistically significant increase was evident in both groups; $P = 0.02$ (Janknegt et al 2001) and $P = 0.013$ (Scheepens et al 2002).

The durability of these outcomes was evaluated in seven patient groups to a maximum follow-up of 60 months. The decreasing sample sizes with longer follow-up and variability of outcomes reporting made it difficult to formally assess durability of effectiveness. Full data tables addressing outcome durability are presented in Appendix I.

The effectiveness of SNS tended to diminish slightly over time; however, statistical significance was maintained in the majority of patient groups for all outcomes. There was no consistent time point for the zenith or nadir of effectiveness across the studies.

Voiding outcomes by lead type

Comparative studies

There were no studies identified which directly compared the effectiveness of tined leads to non-tined leads in SNS for the treatment of detrusor overactivity.

Case series

Data specific to patients with detrusor overactivity implanted with tined leads were reported in three studies for a total of 48 patients (Spinelli et al 2003a; Starkman et al 2007; van Voskuilen et al 2007). Data specific to patients with detrusor overactivity implanted with non-tined leads were reported in three studies for a total of 41 patients (Groenendijk et al 2007; Hedlund et al 2002; Weil et al 2000).

No clear differences between the effectiveness of the two lead types were evident. All outcome measures were appropriately altered by the SNS intervention, with varying levels of statistical significance (Table 17).

Table 17 Efficacy outcomes with the use of tined and non-tined leads for detrusor overactivity

	Tined leads			Non-tined leads		
	Spinelli 2003(a) n=5	**Starkman 2007 n=22**	**van Voskuilen 2007 n=21**	**Groenendijk 2007 n=12**	**Hedlund 2002 n=9**	**Weil 2000 n=20**
Response	80% [a] (4/5)	91% [b] (20/22)	90% [c] (19/21)	83% [b] (10/12)	100% [d] (9/9)	…
Voids/day	Decreased	…	Decreased	…	Decreased	…
P-value	…	…	0.1	…	NS	…
Volume/void	…	…	Increased	…	Increased	…
P-value	…	…	0.001	…	<0.05	…
IE/day	…	…	Decreased	Decreased	…	Decreased
P-value	…	…	0.17	0.002	…	<0.0005
Pad use/day	…	Decreased	…	Decreased	Decreased	Decreased
P-value	…	<0.001	…	0.004	<0.01	<0.0005

NOTES: [a]continence restored & frequency normalised; [b] ≥50% improvement; ≥50% improvement in at least one voiding variable; [d]total continence &/or >50% improvement. 'Increased' or 'Decreased' represents summary measure of comparison pre- and post-implantation. IE incontinent episodes; NS not significant; …not reported

Voiding outcomes by implant method

Comparative studies

One randomised controlled trial comparing one-stage implantation to two-stage implantation was identified (Everaert et al 2004). The underlying indication for SNS was not explicitly clinically defined, but was presented as a combination of 'voiding difficulty' and urge incontinence.

At 24 months follow-up, voided volume was significantly higher (P <0.05), and residual urine significantly lower (P <0.01), in the two-stage group when compared to the one-stage group.

Failure was defined as less than 50 per cent improvement in voided volume or residual urine compared to baseline. Utilising this definition on an intention-to-treat analysis, there was a significantly greater number of failures in the one-stage group (Table 18). Failure was found to be positively related to undergoing a one-stage implant and negatively to the age of the patient, with failing patients significantly younger than successful patients (41±14 years and 53±17 years respectively, P <0.01).

Table 18 Efficacy outcomes with 1-stage and 2-stage implantation (Everaert et al 2004)

	N=	Lost to follow-up	Success	Early failure (<3 months)	Late failure (>3 months)	All failure
1-stage	21	2	12	5	2	7
2-stage	21	0	18	2	1	3
P-value		…	…	…	…	0.02

NOTES: …not reported

Mean quality of life scores related to lower urinary tract symptoms (subjective visual analogue scale (VAS) measurement) were also found to be significantly higher (P <0.05) in the two-stage group at 24 months post-implantation.

Case series

Data specific to patients with detrusor overactivity who underwent screening and implantation of the SNS leads and pulse generator using a one-stage implantation procedure were reported in seven studies for a total of 135 patients (Bosch et al 2000; Edlund et al 2000; Groenendijk et al 2007; Hedlund et al 2002; Latini et al 2006; Roupret et al 2004; Weil et al 2000). Data on patients undergoing a two-stage procedure were reported in four studies for a total of 46 patients (Latini et al 2006; Scheepens et al 2002; Spinelli et al 2003a; Starkman et al 2007). Detailed data on voiding variables presented by implant method are presented in Appendix I.

All voiding variables were improved in both groups after implantation, regardless of the method utilised. Sample sizes were too small, and outcome measures too variable to meaningfully compare the statistical significance of effectiveness outcomes between the two groups.

Quality of life measures

Comparative studies

Three studies reported on quality of life measures in patients with detrusor overactivity utilising the SF-36 survey (Das et al 2004; Hassouna et al 2000; Weil et al 2000) and the Beck Depression Index (BDI) (Das et al 2004).

SF-36 scores reported by Weil et al (2000) and Hassouna et al (2000) assessed only patients with detrusor overactivity. Those reported by Das et al (2004) included the scores of 12 patients with urinary retention randomised to either the control or treatment arms of the study, in addition to those with detrusor overactivity. There was large variability in the scores reported for each of the eight domains, with Das et al (2004) finding significant differences in favour of the treatment group in six domains, Hassouna et al (2000) in seven of the domains and Weil et al (2000) in one domain (Table 19). Weil et al (2000) also reported finding significant differences in the mean physical functioning score and the standardised physical component scale (P =0.034 and 0.019 respectively) when comparing baseline to six month scores in the SNS group.

Table 19 SF-36 quality of life scores at six months

Study		Mean SF-36 Domain scores at 6 months							
		PF	RP	P	SF	MH	RE	V	GH
Das 2004	SNS n= …	66.8±33.0	47.5±45.2	52.5±30.3	66.9±32.1	69.9±21.5	70.0±40.5	47.9±27.9	55.2±26.5
	SMM n= …	36.4±33.5	16.3±31.6	22.6±23.0	38.0±28.4	57.8±26.8	34.7±43.4	29.3±27.5	43.0±24.9
	P=	<0.001	<0.005	<0.001	<0.001	NS	0.002	0.02	NS
Hassouna 2000	SNS n= 25	77	51	60	77	71	62	55	61
	SMM n= 26	48	30	34	43	62	48	36	46
	P=	<0.0001	0.01	0.01	0.002	0.01	0.17 (NS)	0.01	0.003
Weil 2000	SNS n=20	66.6 (55.4-77.7)	59.8 (46.0-73.5)	59.0 (47.5-70.4)	53.8 (49.6-57.9)	68.8 (57.0-80.5)	89.8 (82.3-97.3)	59.5 (48.1-70.8)	62.1 (50.6-73.6)
	SMM n=23	51.1 (38.8-63.4)	58.9 (49.3-68.4)	54.6 (45.1-64.1)	54.9 (49.6-60.2)	67.0 (57.7-76.2)	77.0 (67.4-86.6)	56.3 (46.1-66.5)	56.0 (47.1-65.0)
	P=	NS	NS	NS	NS	NS	0.037	NS	NS

NOTES: PF physical functioning; RP role-physical; P bodily pain; SF social functioning; MH mental health; RE role-emotional; V vitality; GH general health; SNS sacral nerve stimulation; SMM standard medical management; ± standard deviation; ( ) 95% confidence interval; NS not significant; …not reported

BDI scores were reported separately for urge incontinence and urgency-frequency patients by Das et al (2004); however, it was not definitively stated how many patients were evaluated in the treatment and control groups. There were no significant differences observed between the SNS and control groups at baseline for either indication. At 3 months, urge incontinent patients treated with SNS showed a statistically significant decrease in BDI scores (demonstrating improvement in depression measures) compared to the control group (10.0 ±10.0 vs 24.8 ± 17.0, P =0.03). Urgency-frequency patients did not display a significant improvement. There were no significant differences demonstrated between the treatment and control groups for either indication at six months.

Combined data including 28 patients with urge incontinence, 49 with urgency-frequency and 12 with urinary retention showed that 41 per cent of the SNS group were depressed at 3 months post treatment, compared to 73 per cent of the control group ($P < 0.05$).

Case series

Six studies reported a variety of quality of life outcomes for patients with detrusor overactivity (see Appendix I). The four studies that utilised validated quality of life scales specific to urinary incontinence demonstrated statistically significant improvements in patient quality of life at time points up to 18 months post-implantation (Amundsen et al 2002; Amundsen et al 2005; Cappellano et al 2001; Spinelli et al 2001). Subjective symptom improvement was reported as greater than 50 per cent in 77 per cent (33/43) of patients in one study (Aboseif et al 2002) and as a median of 80 per cent improvement in another (Kessler et al 2007). One study also reported on the percentage of patients who stated that they would have the treatment again, with 90 per cent of patients stating that they would undergo the same treatment 18 months post-implantation (Cappellano et al 2001).

Urinary retention

Voiding outcomes

Comparative studies

One study (Jonas et al 2001) compared the outcomes arising from SNS in the treatment of urinary retention to those of standard medical management. Of 68 patients with a positive response to PNE, 37 were randomised to the treatment arm and underwent an early surgical implantation of the SNS system, while the remaining 31 control patients continued with standard medical treatment. Control patients were followed and crossed over into the treatment group at 6 months if an SNS implant remained medically indicated.

Six month efficacy results were available for 29 treatment and 22 control group patients. Comparing the mean differences between the groups, the treatment group showed a significant reduction in the primary voiding diary variable of volume per catheterisation compared to the control group (49±106 mL vs 319±195 mL; P <0.0001). Significant differences in favour of the treatment group in all measured catheterisation variables (number of catheterisations per day, total catheter volume per day and maximum catheter volume) were also observed (P <0.0001 for all variables). Clinically, this represented a decrease in mean catheter volume per catheterisation for SNS patients (49±106mL versus 319±195mL), in the mean number of catheterisations required per day (1.4±2.6 for SNS patients versus 3.9±2.2 for control patients) and in mean total catheterisation volumes per day (237±564mL for SNS patients versus 1305±890mL for control patients).

Patients treated with SNS also increased their number of voids per day (6.5±3.1 versus 2.9±4.3; P =0.002) and total volume voided per day (1808±879 mL versus 488±730 mL, P <0.0001) compared to the control group.

At 18 months, patients were considered to have a successful outcome if they had either eliminated catheterisation or reduced residual volumes by 50 per cent or more. Utilising these criteria, 71 per cent (17/24) of patients evaluated at 18 months were treated successfully with SNS. Catheterisation was completely eliminated in 14 (58%) patients. At this point, patients from the control arm had crossed-over to the treatment group if medically indicated; hence, there were no comparative effectiveness data available.

A total of 34 patients (after crossover) underwent a Therapy Evaluation Test. When stimulation was discontinued, the 34 patients had a statistically significant increase in residual urine (P <0.0001) and decrease in voided volumes (P <0.0002). These results were found to be completely reversible with the reactivation of stimulation.

Case series

The effect of SNS on voiding variables in patients with non-obstructive urinary retention was evaluated in 16 case series. Evaluated groups ranged in size from two to 62 patients, with a median sample size of 21 patients. Follow-up ranged from 3 to 70 months. Complete data on voiding variables for these studies are presented in Appendix I.

Response rates were reported for 11 of the 16 patient groups, and were based on a variety of definitions. A positive response was defined as one of the following: spontaneous voiding; ≥50% improvement in at least one relevant voiding variable;

patients no longer requiring permanent catheterisation; or subjective patient response of 'good' or 'insufficient' response.

Considering the response rate as a generic measure, the rate of positive response to SNS ranged from 50 percent (1/2 patients able to void without permanent or intermittent catheterisation; Groenendijk et al 2007) to 100 per cent (spontaneous voiding in 7/7 patients; Spinelli et al 2003a). The median response rate across all definitions for the 11 patient groups reporting this outcome was 76 per cent.

The number of catheterisations required per day was reported at baseline and post-implantation for seven of the 16 patient groups. Catheterisations per day decreased post-implantation for patients in all seven groups. Significance testing was undertaken for six of these groups; the decrease in catheterisations was found to be statistically significant in four of the six ($P<0.02$).

The volume of urine per catheterisation was assessed in five patient groups, with a decreased volume found in all five. This was reported as statistically significant in four of these groups.

The number of voids per day was also reported for four of the patient groups. An increase in unassisted voids was reported in three of these groups. However, these changes were statistically significant in only one of the four groups ($P<0.001$; Spinelli 2005). The volume of urine per void post-implantation was also assessed in comparison to baseline volumes in three patient groups. There was an increased volume per void in all of these groups, which was found to be statistically significant in two. Post-void residual volume (PVR) was reported for three patient groups, with a decrease in all groups. This result was tested for significance in only one group ($P<0.05$; Aboseif et al 2002).

Voiding outcomes by lead type

Comparative studies

There were no studies identified that directly compared the effectiveness of tined leads to non-tined leads in SNS for the treatment of urinary retention.

Case series

Data specific to patients with urinary retention implanted with tined leads were reported in three studies for a total of 47 patients (Datta et al 2008; Spinelli et al 2003a; van Voskuilen et al 2007). Data on patients with non-tined leads implanted were reported in two studies for a total of 32 patients (Datta et al 2008; Groenendijk et al 2007).

Small sample size and a lack of consistent outcomes reporting resulted in there being no clear differences between the effectiveness of the two lead types evident in this dataset (Table 20)

Table 20 Effect of tined and non-tined leads on voiding outcomes (retention)

	Tined leads			Non-tined leads	
	Datta 2008 n=30	Spinelli 2003a n=7	van Voskuilen 2007 n=10	Datta 2008 n=30	Groenendijk 2007 n=2
Response	73%[a] (22/30)	100% [a] (7/7)	90%[b] (9/10)	70% [a] (21/30)	50%[c](1/2)
Cath./day	…	Decreased	Decreased	…	…
P-value	…	…	NS	…	…
Volume/cath.	…	…	Decreased	…	…
P-value	…	…	NS	…	…
Mean PVR	…	Decreased	…	…	…
P-value		…	…	…	…
Voids/day	…	…	Increased	…	…
P-value	…	…	NS	…	…
Volume/void	…	…	Increased	…	…
P-value	…	…	NS	…	…

NOTES: [a] spontaneous voiding; [b] ≥50% improvement in presenting symptoms; [c] able to void without any catheterisation. 'increased' or 'decreased' represents summary measure comparison pre- and post- SNS implantation; cath catheterisations; PVR post-void residual; NS not significant; …not reported

Voiding outcomes by implant method

Comparative studies

There were no studies directly comparing the effectiveness of one-stage implantation to two-stage implantation in SNS for the treatment of urinary retention identified.

Case series

Data specific to patients with urinary retention who underwent screening and implantation of the SNS leads and pulse generator using a one-stage implantation procedure were reported in three studies for a total of 61 patients (Datta et al 2008; Groenendijk et al 2007; Jonas et al 2001). Data on patients undergoing a two-stage procedure were reported in three studies for a total of 44 patients (Datta et al 2008; Scheepens et al 2002; Spinelli et al 2003a).

While both groups achieved statistical significance across a range of voiding variables, neither implantation method displayed clear superiority over the other across this dataset (Table 21). Inconsistent outcomes reporting prevented any clinically relevant comparisons between the two groups.

Table 21 Voiding outcomes by implant method

	1-stage implantation			2-stage implantation		
	Datta 2008 n=30	Groenendijk 2007 n=2	Jonas 2001 n=29	Datta 2008 n=30	Scheepens 2002 n=7	Spinelli 2003a n=7
Response	70% [a] (21/30)	50% [b] (1/2)	…	73% [a] (22/30)	…	100% [a] (7/7)
Cath./day	…	…	Decreased	…	Decreased	Decreased
P-value	…	…	<0.0001	…	0.024	…
Volume/cath.	…	…	Decreased	…	Increased	…
P-value	…	…	<0.0001	…	0.027	…
PVR	…	…	…	…	…	Decreased
P-value	…	…	…	…	…	…
Voids/day	…	…	Increased	…	…	…
P-value	…	…	0.002	…	…	…
Volume/void	…	…	Increased	…	Increased	…
P-value	…	…	<0.0001	…	0.017	…

NOTES: [a] spontaneous voiding; [b] able to void without any catheterisation. 'Increased' or 'Decreased' represents summary measure comparison pre- and post-implantation. Cath catheterisation; PVR post-void residual; …not reported

Quality of life measures

Comparative studies

The one comparative study evaluating SNS in the treatment of urinary retention (Jonas et al 2001) did not report quality of life outcomes.

Case series

Quality of life measures were reported for two patient groups. Kessler et al (2007) reported a median 85 per cent improvement in symptoms (range: 51-100%) at final follow-up, based on subjective patient response. Ninety per cent of patients (18/20) reported greater than 50 per cent improvement in quality of life post-implantation; however, the scale utilised was not stated (Aboseif et al 2002).

Painful bladder syndrome

Voiding outcomes

Comparative studies

No comparative studies addressing the effectiveness of SNS in the treatment of painful bladder syndrome (PBS) were identified.

Case series

Six case series reported data on the effectiveness of SNS in the treatment of PBS. One other study reported on patients with detrusor overactivity and concomitant pelvic pain (Aboseif et al 2002). The sample size of the six case series ranged from four to 26 patients, with a median sample size of 16.

There were statistically significant decreases in both voids per day and nocturia episodes in the three studies that reported on these variables (P <0.01). Only one study reported on volume per voids, but this was found to be significantly decreased post-implantation (P <0.01; Comiter et al 2003).

Changes in pain levels post-implantation were documented in a variety of ways by the four studies reporting this outcome. Two studies utilised a scale of one to 10 for patients to rate their pain level, and both reported significantly decreased pain post-implantation (P <0.01, Comiter et al 2003; P =0.03, Kessler et al 2007). One study stated that 71 per cent of patients 'reported less pain' after SNS (Peters et al 2003). Peters et al (2004) utilised the mean narcotic dose required by patients pre- and post-implantation as a measure of effectiveness. A significant decrease in narcotic requirement post-implantation was noted. (81.6mg/day vs 52.0mg/day mean narcotic dose intramuscular morphine dose equivalent, P =0.015).

Voiding outcomes by lead type

Comparative studies and case series reporting data on patients with painful bladder syndrome did not report the type of leads utilised.

Voiding outcomes by implant method

No comparative studies or case series reporting data specific to patients with PBS who underwent screening and implantation of the SNS leads and pulse generator using a one-stage or two-stage implantation procedure were identified.

Quality of life measures

Comparative studies

No comparative studies addressing the effectiveness of SNS in improving quality of life measures in patients with PBS were identified.

Case series

Comiter et al (2003) utilised the Interstitial Cystitis Symptoms Index and the Interstitial Cystitis Problem Index to quantify the effect of SNS on quality of life. Both of these measurements were found to be significantly reduced post-implantation (P <0.01), with a decrease in mean scores from 16.5 to 6.8 and 14.5 to 5.4 respectively when measured at a mean follow-up of 14 months.

Summary of effectiveness outcomes

- Comparative data from crossover trials in patients with detrusor overactivity and non-obstructive urinary retention demonstrated consistently statistically significant and clinically notable improvements favouring those treated with sacral nerve stimulation over those receiving standard medical management across a range of voiding outcomes. Effectiveness of SNS was maintained beyond 6 months in implanted patients.

- Non-comparative data from the available case series demonstrated that sacral nerve stimulation affords an overall benefit in terms of continence status for patients with refractory detrusor overactivity (23 studies; 981 patients) and non-obstructive urinary retention (16 studies; 433 patients).

- Non-comparative data from 90 patients, reported in six case series, showed that symptoms associated with painful bladder syndrome (increased voiding, nocturia and pain) were reduced by sacral nerve stimulation.

- Sample sizes were too small and outcome measures too variable to meaningfully compare the effectiveness of tined leads to non-tined leads and one-stage implantation to two-stage implantation for any indication.

- The impact of quality of life demonstrated by SNS in patients with detrusor overactivity, non-obstructive urinary retention and painful bladder syndrome is positive, but not yet definitive.

- More data are required before the long-term durability of the procedure and device can be adequately assessed; however, the available data support the continued effectiveness of SNS beyond 3 years.

From the limited data available, sacral nerve stimulation appears to be an effective treatment for the voiding disruptions associated with detrusor overactivity and non-obstructive urinary retention. It shows positive outcomes in the small number of patients with painful bladder syndrome treated thus far.

What are the economic considerations?

Economic evaluation of new healthcare technologies is important when determining whether the new initiative offers additional benefits and at what cost. Economic evaluations are able to determine whether the new initiative is dominated by (or dominates) the existing technology, such that the costs are higher (lower) and the effectiveness is less (greater). Economic evaluation is particularly important where the new initiative offers health benefits at additional costs. Within a constrained healthcare budget, determining the additional cost that would be paid for a given health gain is important when ascertaining whether such incremental costs represent value for money.

The usual process for an economic evaluation is first to determine the incremental effectiveness, which is the additional benefits associated with the new technology relative to current practice. Secondly, to determine the incremental costs; this is the difference in costs between the new initiative and the comparator. Finally, the incremental cost-effectiveness ratio (ICER) can be calculated using the following ratio:

$$ICER = \frac{Cost_{New} - Cost_{Comparator}}{Effectiveness_{New} - Effectiveness_{Comparator}}$$

To allow comparison of effectiveness in one area with effectiveness in another, it is preferable for an economic evaluation to undertake a cost-utility analysis. A cost-utility analysis generates an ICER as described above, using a generic outcome measure, defined as one which can be utilised in different areas of healthcare. The most common generic outcome measure is the quality-adjusted life year (QALY). This is a measure of effectiveness which combines morbidity and mortality dimensions into one composite measure of outcome. The use of cost-utility analysis, while preferable to disease-specific outcome measures, is reliant on the existence of appropriate published data. This includes generic quality of life measures, such as the SF-6D, the SF-36 or the EQ-5D.

Published evidence on the cost-effectiveness of SNS

Search strategies

Databases of peer-reviewed literature including Medline, PubMed, CINAHL and Cochrane were searched. The bibliographies of all retrieved publications were hand-searched for any relevant references missing in the database search. Web-based searches included the Internet engines 'Google' and 'Google scholar'.

In addition to the search terms described in the 'approach to assessment' section, Cost$ or Econ$ were added. This was to identify any published cost-effectiveness analysis. The inclusion and exclusion criteria remained the same.

There is a limited body of published evidence concerning the cost-effectiveness of SNS compared to conservative, non-surgical treatment for the indications being considered. The original MSAC report of sacral nerve stimulation for refractory urge incontinence or urinary retention (MSAC Application 1009, 2000) found that, on the strength of the evidence pertaining to sacral nerve stimulation:

- the intervention is associated with a relatively high rate of adverse events (Number Needed to Harm(NNH)=2);
- the long-term effectiveness is uncertain;
- the cost-effectiveness ratios associated with the intervention are unfavourable.

Consequently an MSAC report for sacral nerve stimulation for faecal incontinence (MSAC Application 1077, 2005) found that there is some evidence of effectiveness and cost-effectiveness for this indication. The economic evaluation was subject to many limitations, including the use of data from case series and considerable uncertainty in relation to costs.

The literature search conducted as part of this evaluation identified one Health Technology Assessment (HTA) undertaken by the Ontario Health Technology Advisory Committee (OHTAC) in 2005 for urinary urge incontinence, urgency-frequency, urinary retention and faecal incontinence. The report concluded that there was Level II evidence indicating that sacral nerve stimulation is effective in patients with urge incontinence, urgency-frequency and urinary retention (Ontario MAS 2005).

None of the studies in this report followed patients until the point of battery failure; however while the long-term data is limited, there is Level IV data indicating the device is effective up to 5 years. However, a high revision rate (33%) was reported in the analysis of the safety of three RCTs comparing SNS to no treatment in patients with urge incontinence, urgency-frequency or urinary retention (Ontario MAS 2005).

Two costs analyses, one in faecal incontinence and one in voiding dysfunction, were also found (Hetzer et al 2006; Aboseif et al 2007).

Rationale for the cost-effectiveness analysis

For detrusor overactivity and urinary retention, we identified evidence suitable for use in economic evaluation. Therefore, the results presented here are cost-effectiveness analyses. For painful bladder syndrome, this was not possible. Therefore, the costs alone are considered, and are comparable to those identified for detrusor overactivity, but differ slightly to those for urinary retention as the cost-offset associated with self-catheterisation is higher than the offset for pads and other items in the former groups.

Assumptions

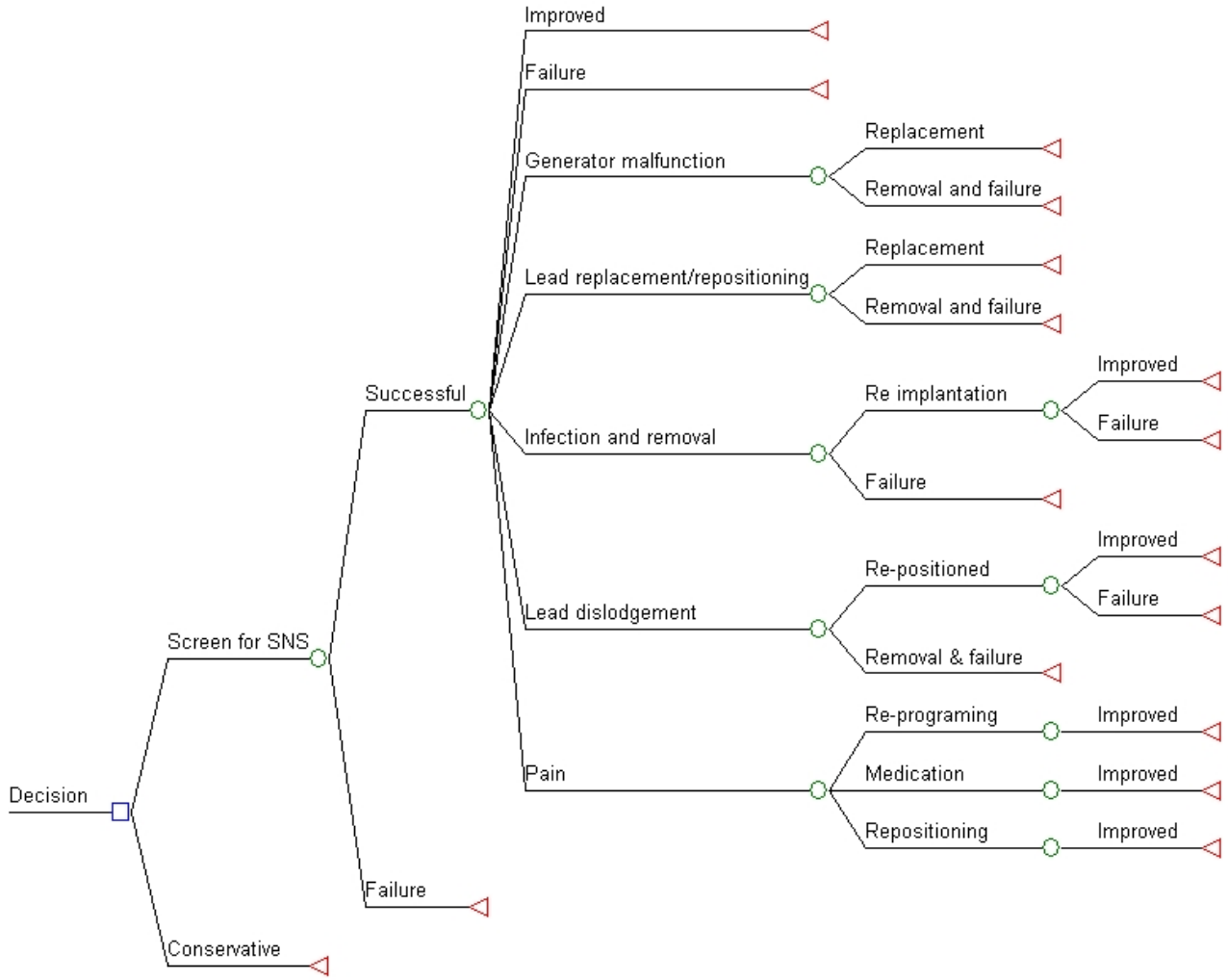
- As patients are assumed to have failed conservative therapy, the comparator was assumed to be 'conservative therapy' for all indications. However, as noted below, the costs of this comparator are potentially large.
- The time horizon was the average battery life, estimated to be 7 years (Source: Medtronic Australia).
- The perspective of the cost-effectiveness analysis is limited to the costs faced by the healthcare system and by the individual directly relating to dealing with adverse effects (such as the costs associated with incontinence pads or catheterisation).
- A discount rate of five per cent per annum was applied to all costs.

- While all of the individuals in the intervention arm receive PNE, only 47.72 per cent of these go on to receive SNS.

Structure of the economic evaluation

The possible outcomes associated with PNE and SNS are given in Figure 4. Following the decision to enter PNE for SNS, those who are screened may or may not be suitable for SNS treatment. For this group, there are a variety of adverse events which can occur. The consequences of the adverse events are also given. All costs and outcomes in each branch of the tree are evaluated, and multiplied by the likelihood of an individual progressing into that branch. By summing these costs and outcomes, the expected costs and outcomes associated with using the two technologies can be estimated. Note also that this diagram is a slight simplification in that we allow an individual to have more than one of these adverse events.

Figure 4 Structure of the economic evaluation



Estimates of costs

The cost of the procedure for all urinary indications was the same for stage I PNE and stage II SNS. The costs are broken down into the hardware costs, MBS costs per patient related specifically to SNS, other surgical costs, costs of complications, and cost reductions associated with reduced incontinence pad use following successful SNS for detrusor overactivity and catheterisation for urinary retention.

The breakdown of hardware costs are outlined in Table 22.

Table 22 Hardware costs*

Item	Cost $A	Cost $A + GST
PNE†		
PNE Kit	385.00	423.50
Test stimulation lead	130.00	143.00
Total cost	**515.00**	**566.50**
SNS		
Tined lead	4,330.00	4,763.00
Lead introducer kit	541.00	595.00
Quadripolar extension kit	2,138.00	2,352.00
Interstim IPG	9,350.00	10,285.00
Patient programmer	1,318.00	1,450.00
Foramen needles	130.00	143.00
Total cost	**17,807.00**	**19,588.00**

NOTES: *Cost provided by applicant; † Following Advisory Panel guidance, this excludes the external stimulation power source @ $550 as this is usually provided by the company; PNE peripheral nerve evaluation; SNS sacral nerve stimulation; IPG implantable pulse generator; GST Goods and Services Tax

Direct treatment costs per procedure

The direct treatment costs per procedure are estimated in Table 23 for PNE and Table 24 for SNS.

Table 23 Unit costs associated with PNE in a private hospital facility

Item	Cost $A	Source
Cost of equipment (PNE Kit and lead)	566.50*	Medtronic Australia
Medical fee	596.90	MBS Item 32213 (Placement of sacral nerve leads)
Imaging fee	29.75	MBS Item 60503 (Fluoroscopy)
Local anaesthesia	80.05	MBS Item 18274 (Sacral nerve anaesthesia)
Hospital facility	823.60	Average same day procedure cost for private hospitals; National Hospital data Collection Weights from AR-DRG Version 4.2, Round 7, 2002-3 indexed to 2006
Follow up visits (1)	38.80	MBS item 105
Total	**2135.60**	

NOTES: * This cost excludes the external stimulation power source as this was usually provided by the manufacturer; PNE peripheral nerve evaluation; MBS Medicare Benefits Schedule

Table 24 Unit costs associated with SNS in a private hospital facility

Item	Cost $A	Source of cost
Cost of equipment	19,588.00	Medtronic Australia
Medical fee	301.55	MBS item 32214 (Subcutaneous placement of neurostimulator)
Anaesthesia initiation	80.05	MBS item 18274 (Sacral nerve anaesthesia)
Anaesthesia time units	89.50	MBS item 23051 1:01 hours to 1:05 hours
Hospital facility	823.60	Average same day procedure cost for private hospitals; National Hospital data Collection Weights from AR-DRG Version 4.2, Round 7, 2002-3 indexed to 2006
Follow up visits (3)	116.40	MBS item 105 ($38.80) (Ontario HTA report)
Total	**20,999.10**	

NOTES: MBS Medicare Benefits Schedule

Costs and occurrence of complications

The complications considered in this economic evaluation are the following:

- lead dislodgement/migration
- generator malfunction
- lead replacement
- pain requiring treatment
- infection.

The proportion of SNS patients with each of these complications across all indications has been previously identified in Table 11. As the rate of complications is likely to be comparable across indications, the economic evaluation uses the pooled data. This is presented alongside the assumed costs and outcomes in Table 25.

Table 25 Rate and consequences of complications in SNS

Complication	Probability	Cost item	Cost	Source
Lead dislodgement / migration	7.29%	Same day surgery facility	$823.60	Average same day procedure cost for private hospitals; National Hospital data Collection Weights from AR-DRG Version 4.2, Round 7, 2002-3 indexed to 2006
		Medical cost	$536.05	MBS 32216
Generator malfunction	3.77%	Same day surgery facility	$823.60	Average same day procedure cost for private hospitals; National Hospital data Collection Weights from AR-DRG Version 4.2, Round 7, 2002-3 indexed to 2006
		Medical cost	$230.70	MBS 3660 (Removal and replacement of pulse generator)
Lead replacement / repositioning	16.50%	Same day surgery facility	$823.60	Average same day procedure cost for private hospitals; National Hospital data Collection Weights from AR-DRG Version 4.2, Round 7, 2002-3 indexed to 2006
		Medical cost	$551.10	MBS 3662 (Removal and replacement of leads)
Pain at IPG site requiring treatment	14.28%	Medical cost	$115.45	MBS 39131
Infection	5.63%	Medical cost	$115.45	MBS 39131
		Removal of implant	$230.70	MBS 3660 (Removal and replacement of pulse generator)
		Reimplantation (covering all SNS costs)	$20,999	Table 24
		Pharmacotherapy and hospital stay	$3,277.61	2-3 day Hospital stay + IV treatment (Meropenem 1g IV @ $56.45 per 1g 8 hourly plus Lincomycin 600mg IV @ $25.40 per 600mg 8-hourly) + 3 weeks of oral antibiotics (e.g. Dicloxacillin @ $17.54 per pack of 24 (acquisition cost source PBS and hospital pharmacy dispensing system)
Expected costs of complications per SNS patient				**$1,768**

NOTES: MBS Medicare Benefits Schedule; IPG implantable pulse generator; IV intravenous; SNS sacral nerve stimulation

Personal costs

Detrusor overactivity

Dowell et al (1999) reported that personal costs for urinary incontinence were $291.72 per woman per annum. For this report, this has been indexed to 2008 costs using ABS data on the Retail Price Index, giving a value of $394.23 per annum. In both the control and the intervention group, it is assumed these costs are incurred unless the patient is completely dry (for those with detrusor overactivity) or responding well (for those with urinary retention).

Urinary retention

The major personal costs associated with urinary retention are those of self-catheterisation, and apply to those who do not respond in the intervention arm, and those in the control group. Jonas et al reported a reduction of 2.5 catheterisations per day in their intervention group (1.4 per day versus 3.9 per day). Using costs taken from Bright Sky Australia (Conveen Nelaton® catheter female or male) of $1.00 per catheter,

this additional cost of catheterisation over 7 years (discounted at five per cent per annum) is $5,544.07.

Painful bladder syndrome

As per Advisory Panel suggestion, it was assumed that all non-respondents in both the intervention and the control used pentosan polysulphate sodium (Elmiron®) 100mg. Assuming 300 mg/day, and a cost of $125 per 100 capsule bottle, the cost per annum is $1,369.

Clinical outcomes for use in the economic evaluation

For the economic evaluation, we have to identify the outcome which is most representative of improvement in the population group (be it detrusor overactivity or urinary retention). The candidates from the trials with the highest level of evidence are presented below. The outcome measures selected for the economic evaluation are presented in **bold**.

Table 26 Clinical effectiveness figures for economic evaluation

Indication	Reference	Outcome measure	Horizon	Result	P value
Detrusor overactivity	Hassouna et al 2000	Number of daily voids	6 months	16.9 to 9.3	<0.0001
		Volume per void	6 months	118 ml to 226 ml	<0.0001
		(Average) degree of urgency	6 months	2.2 to 1.6*	<0.0001
		SF-36 score	6 months	All dimensions improved	Maximum of 0.17
	Weil et al 2000	**Complete dryness**	**6 months**	**56% vs. 4% (control)**	
		Leakage episodes	6 months	88% reduction	<0.0005
		Leakage severity	6 months	24% reduction	0.047
		Pad usage	6 months	90% reduction	<0.0005
Urinary retention	Jonas et al 2001	Catheter volume per catheterisation	6 months	-290 ml vs. -31 ml (control)	<0.0001
		Catheter removal	6 months	69%	Not stated
		Successful results†	**6 months**	**83% vs. 9% in control**	**Not stated**
		Voids per day	6 months	+2.5 vs. -0.3 (control)	0.002
		Total volume voided per day	6 months	+1,086 ml vs. -72 ml	<0.0001

NOTES: * Degree of urgency measured by 0 = none, 1 = mild, 2 = moderate 3 = severe † Catheterisation eliminated or 50% reduction in catheter volume per catheterisation

These outcomes are achieved using a population of responders to PNE. For those who enter PNE the expected outcome is less, as 52 per cent fail PNE and revert to conservative management, and a number do not successfully respond following implantation. Therefore, the expected benefit of SNS for detrusor overactivity and urinary retention has to be multiplied by the proportion who successfully respond at both stages. For detrusor overactivity, this means that the additional 52 per cent of individuals who achieve complete dryness in the intervention has to be multiplied by the probability of passing PNE (47.72%) to give the additional probability of achieving complete dryness for someone entering PNE.

For urinary retention, the same approach has to be taken; the additional 74 per cent of people achieving successful results has to be multiplied by the same figure (47.72%). For the cost-effectiveness analysis, the primary outcome is presented in terms of years of dryness or years with successful results over the 7 year time horizon. As with costs, these outcomes are discounted at five per cent per annum.

The summary of the incremental costs are presented below, and combined with these new clinical outcomes to produce baseline incremental cost-effectiveness ratios. In addition, the incremental cost of SNS for painful bladder syndrome is outlined, and is identical to that given for detrusor overactivity.

Table 27 Incremental cost-effectiveness of performing SNS for detrusor overactivity (base case)

Items	Sacral nerve stimulation (SNS)		Conservative treatment		Incremental cost of SNS per patient
	Units/patient	Cost A$	Units/patient	Cost A$	
Procedure (PNE)	1	2,135.60	0	0	2,135.60
Procedure (SNS)	0.4772	20,999.10	0	0	10,020.77
Complications	0.4772	1,768.44	0	0	843.90
Personal costs*	0.7519	2,395.22	0.96	2,395.22	-498.55
Incremental cost of SNS per patient					**12,501.72**
Primary outcome					
	Complete dryness	24.81%		4%	20.81%
	Discounted years of complete dryness				1.2419
Cost-effectiveness ($ per additional patient year with complete dryness)					**$9,866**

NOTES: * Dowell et al 1999; PNE peripheral nerve evaluation

Table 28 Incremental cost-effectiveness of performing SNS for urinary retention (base case)

Items	Sacral nerve stimulation (SNS)		Conservative treatment		Incremental cost of SNS per patient
	Units/patient	Cost A$	Units/patient	Cost A$	
Procedure (PNE)	1	2,135.60	0	0	2,135.60
Procedure (SNS)	0.4772	20,999.10	0	0	10,020.77
Complications	0.4772	1,768.44	0	0	843.90
Personal costs	0.6469	5,544.07	0.91	5,544.07	-1,458.64
Incremental cost of SNS per patient					**11,541.63**
Primary outcome					
	Successful result*	35.31%		9%	26.31%
	Discounted years of successful results				1.5985
Cost-effectiveness ($ per additional patient year with successful results)					**$7,219**

NOTES: * Catheterisation eliminated or 50% reduction in catheter volume per catheterisation; PNE peripheral nerve evaluation

Table 29 Incremental cost of performing SNS for painful bladder syndrome (base case)

Items	Sacral nerve stimulation (SNS)		Conservative treatment		Incremental cost of SNS per patient
	Units/patient	Cost A$	Units/patient	Cost A$	
Procedure (PNE)	1	2,135.60	0	0	2,135.60
Procedure (SNS)	0.4772	20,999.10	0	0	10,020.77
Complications	0.4772	1,768.44	0	0	843.90
Personal costs	0.7519	8,318	0.96	8,318	-1,700.12
Incremental cost of SNS per patient					**11,300.15**

Sensitivity analysis

A univariate analysis was undertaken, considering the effect of changing variables suggested by the Advisory Panel as being either most likely to affect the result, or most uncertain. The ranges investigated are largely arbitrary, so the interpretation of the result is based more on the rate at which the base case changes, rather than the absolute numbers given. The variables considered, the bands used for sensitivity analysis, and the ICER (or cost) of SNS for each of the three indications under consideration are given in Table 30.

Table 30 Univariate sensitivity analysis

Variable	Base case	Band used for sensitivity analysis	ICER (detrusor overactivity)	ICER (urinary retention)	Cost (PBS)
Base case result			$9,886	$7,219	$11,269
Conversion rate from PNE to SNS	47.72%	37.72% - 57.72%	$9,159 - $11,096	$5,434 - $10,401	$9,425 - $13,113
Adverse events	Rates differed by event (see Table 25)	All events occur with a frequency of ±10%	$9,819 - $9,952	$7,167 - $7,272	$11,185 - $11,353
Catheterisation costs	$5,544.07	±$2,000 over 7 years	NA	$6,890 - $7,549	NA
Personal costs for detrusor overactivity	$2,395.22	±$2,000 over 7 years	$9,557 - $10,215	NA	NA
Medication costs for PBS	$8,317.62	±$2,000 over 7 years	NA	NA	$10,853 - $11,685
Total cost of SNS	$20,999.10	$10,999.10 - $30,999.10	$6,112 - $13,659	$4,234 - $10,204	$6,497 - $16,041
Total cost of PNE	$2,135.60	$1,135.60 - $3,135.60	$9,095 - $10,677	$6,594 - $7,845	$10,269 - $12,269

NOTES: ICER incremental cost-effectiveness ratio; PBS painful bladder syndrome; PNE peripheral nerve evaluation; SNS sacral nerve stimulation; NA not applicable

Financial implications

The expected number of patients to be treated with PNE (of which a proportion will go on to receive SNS) per year is 200, although the likelihood of 200 in the first year is small due to lack of capacity in the field. If these 200 patients were divided equally amongst the three indications considered (detrusor overactivity, urinary retention and painful bladder syndrome) and the conversion rate from PNE to SNS is assumed to be constant across indications, the economic analysis presented here predicts a total net cost of $2.356 million per annum. This consists of costs incurred by the healthcare system (PNE, SNS and dealing with complications), which sum to $2.600 million, minus the cost reduction associated with reduced use of catheters, pads etc. by the individual ($244,000).

However, expert clinical opinion suggests that the division of patients amongst the indications is not likely to be equal; rather it is anticipated that 90 per cent of patients would present with detrusor overactivity and 10 per cent with urinary retention. Should this be the case, the total net cost would be $2.481 million per annum. This consists of costs incurred by the healthcare system (PNE, SNS and dealing with complications), which sum to $2.600 million, minus the cost reduction associated with reduced use of catheters, pads etc. by the individual ($119,000).

What are the other considerations?

Alternative treatments

There were no studies identified that utilised operative procedures as direct comparators to the SNS procedure. However, the Advisory Panel felt it important to note that SNS is indicated only for patients who have not responded to, or have not tolerated, the available pharmacological and physiological interventions. Hence, the operative alternatives for this population are significantly more invasive than SNS. Further, they all carry the potential for complications, may also require revision and, unlike SNS, are usually not reversible if unsuccessful.

Botulinum toxin

Botulinum toxin, injected into the detrusor muscle or bladder wall to temporarily paralyse the muscle, is being used with increasing frequency to treat refractory detrusor overactivity and painful bladder syndrome. Currently in Australia, the use of botulinum toxin for these indications is not TGA approved, publicly funded or endorsed by the Department of Health and Ageing.

Botulinum toxin is only suitable for use in patients who are willing and able to self-catheterise. The duration of benefit ranges from between three to 12 months, at which point repeat injections are required to maintain effectiveness (National Collaborating Centre for Women's and Children's Health (NCCWCH) 2006). Common adverse effects and complications (reported in more than 10 per cent of patients) include haematuria, pelvic pain, transient dysuria, transient retention, difficulty urinating, a feeling of incomplete emptying and urinary tract infection (NCCWCH 2006).

Augmentation cystoplasty

Augmentation cystoplasty is a complex and non-reversible procedure that is used for the treatment of a variety of incontinence indications in males and females including detrusor overactivity (idiopathic and neurogenic) and stress incontinence. It aims to increase the functional capacity of the bladder by bivalving the bladder wall and incorporating a segment of bowel. Long-term effectiveness of this procedure is variable and may be dependent on patch revision or further surgery (NCCWCH 2006). Common and serious complications include: bowel disturbance; metabolic acidosis; mucus production and/or retention in the bladder; urinary tract infection; and urinary retention. There is also a small, but serious, risk of malignancy occurring in the augmented bladder, which requires cystoscopic surveillance (NCCWCH 2006).

Urinary diversion

Urinary diversion may be undertaken in the form of a urostomy or continent diversion. A urostomy involves the diversion of urine through a stoma created in the abdominal wall. Urine is collected in a collecting pouch that covers the stoma opening (NIDDK 2006). A continent diversion involves the creation of a pouch or reservoir inside the body from a section of stomach or intestine. The ureters carry urine to the pouch, where it is stored and later emptied – the method for emptying depends on the type of continent diversion (NIDDK 2006).

There are limited data on the outcomes of urinary diversion in women with urge incontinence or overactive bladder. Limited data from studies of men and women receiving diversion for benign conditions have shown that vesicle infection, stoma-related problems and the need for surgical revisions occur very commonly (NCCWCH 2006).

Permanent indwelling catheter

Some patients with non-obstructive urinary retention may manage their urinary dysfunction through the use of a permanent indwelling catheter. The primary risk of long-term use is infection; the risk of developing a catheter-related urinary tract infection can reach up to 20 per cent in individuals with indwelling catheters with closed drainage systems. Long-term catheterisation also poses a risk of chronic renal inflammation, chronic pyelonephritis, development of calculi and symptomatic UTI that may lead to bacteraemia, sepsis and death (North West Melbourne Division of General Practice 2006).

Personnel and skill/experience required

The physician performing the SNS implant must be specifically trained in the use of the SNS device and proficient in parameter adjustment of the device in order to maximise the clinical effectiveness. Expert opinion from the Advisory Panel indicated that there may be a learning curve associated with this procedure, and emphasised the need for practitioners to undergo appropriate training, mentoring and skills maintenance.

Consumer perspective

Quality of life

Overall, the effect of SNS on quality of life outcomes was poorly reported. Three studies employed the SF-36 survey across eight domains to assess differences in quality of life scores between patients receiving an SNS implant and those continuing standard medical management for detrusor overactivity and urinary retention (Das et al 2004; Hassouna et al 2000; Weil et al 2000). The results did not consistently favour one treatment over the other. One study used the Beck Depression Index (BDI) as a measure of quality of life in patients with detrusor overactivity and urinary retention (Das et al 2004). While depression levels declined in the SNS group initially, at 6 months post-treatment there were no significant differences in depression levels demonstrated between the SNS and control groups.

Case series data from patients treated with SNS for urinary retention showed that 18 of 20 patients reported a greater than 50 per cent improvement in quality of life post-implantation; however, the scale utilised was not stated (Aboseif et al 2002).

Utilising the Interstitial Cystitis Symptoms Index and the Interstitial Cystitis Problem Index, one study found these measurements to be significantly improved post-implantation in patients with painful bladder syndrome (Comiter et al 2003).

Patient costs

Effective treatment of incontinence with SNS may help to defray the costs associated with incontinence that are borne solely by the individual and not the healthcare system. This may include the cost of washing/replacing clothing, incontinence pads and other

personal care items and the loss of income associated with decreased workforce participation. Specific detail regarding these aspects of incontinence was not examined within the included studies.

The role of the SNS procedure

SNS represents a considerably less invasive option than other operative alternatives should a patient's incontinence prove to be refractory to standard pharmacological and physical therapies. SNS also has the benefit of being reversible at any stage without serious complications should the patient change their mind or the device lose its effectiveness. In this way, SNS provides an important intermediary addition to the treatment options for refractory incontinence.

Screening and implantation

Patients should be made aware of the need for two procedures as part of SNS – the initial screening test, followed by permanent implantation should the patient exhibit a positive response to screening. The accuracy of the screening test has improved with the change to tined leads; however, treatment options available to patients should they fail screening must also be clearly explained.

Patients should also be made aware of the potential complications of the procedure. The majority of these are minor in nature (non-specific pain, superficial infection etc), but others, such as lead migration and deep infection, may require removal or revision of the device.

Findings of previous MSAC report (Application 1009)

Comparison of safety findings

While the modifications to the device and surgical procedure for SNS, and resultant changes to the patterns of outcome reporting have precluded the pooling of evidence from pre- and post-2000, some general comparisons between the two datasets are considered below.

The need for lead replacement/repositioning was the most frequently reported adverse event across the current body of evidence, occurring in approximately 16 per cent of the 1444 patients for whom this outcome was reported (95% CI: 14.71-18.67). These revisions were often undertaken in an effort to optimise the clinical effectiveness of the SNS device, in the absence of definitive evidence of lead migration. However, there was no comparable outcome reported in Application 1009 (MSAC 2000).

Lead/electrode migration was reported in 6.98 per cent of 1561 patients (95%CI: 5.72-8.24). The comparable outcome reported in Application 1009 was that of 'lead problems', at a rate of 16.5 per cent across 248 patients (95% CI: 12.1-21.8). This reduction may reflect the impact of the 2002 introduction of the tined lead, purported to reduce the incidence of post-implantation lead migration.

The only clinical adverse event with comparable data reported in Application 1009 was infection. Rates of infection are lower in the current evidence base (5.83 per cent across 1303 patients versus 9.9 per cent across 233 patients).

Rates of device removal were similar in the two reports, and no mortality directly associated with chronic SNS has been reported.

Comparison of effectiveness findings

The current application employs a larger evidence base than that of Application 1009. The best available current evidence is provided by three RCTs, which have some methodological weaknesses limiting the strength of their results. On the basis of this evidence, SNS appears to offer treatment benefits to patients with detrusor overactivity and non-obstructive retention, with a consistent trend towards statistically significant results favouring SNS over standard medical management. These findings confirm and strengthen the evidence found for the treatment benefits which were described in Application 1009. However, the impact of SNS on quality of life remains poorly defined.

Further, the volume of evidence from case series published from 2000-2007 is substantially larger than that available for Application 1009. While the potential biases inherent in case series data should not be overlooked, the weight of supportive evidence for SNS in the treatment of detrusor overactivity and urinary retention is considerable.

Expert opinion

Use of SNS for the treatment of painful bladder syndrome

Members of the Advisory Panel expressed concerns surrounding the lack of long-term follow-up data available on patients with painful bladder syndrome. For this indication, SNS is employed primarily for pain management; there is no evidence that it treats the underlying pathology of PBS.

Medicare descriptors

Advisory Panel members highlighted that the current terms used to describe the indications for SNS ('urinary incontinence' and 'urge retention'; MBS item numbers 36658, 36660 and 36662) are inaccurate. As they currently read, these item descriptors can be interpreted to include other forms of incontinence, such as stress incontinence, that are not expected to respond to treatment with SNS. Any addition to the MBS for this procedure should be described in a manner that reflects the precise indications for SNS as considered by this report, namely detrusor overactivity and urinary retention.

Discussion

Limitations of the evidence

This review of the safety and effectiveness of chronic therapeutic sacral nerve stimulation for the treatment of detrusor overactivity, non-obstructive retention and painful bladder syndrome was limited by the quantity and quality of the available evidence.

The evidence base was dominated by studies using discordant outcome measures across a variety of patient populations. The few randomised controlled trials available provided limited comparative data, due to the ethical imperative of crossing patients over from the control to the treatment group after 6 months if still medically indicated. Additionally, the choice of comparator, standard medical management, does not share the same risks of adverse events that arise from a surgical procedure, further limiting the opportunities for genuine comparison between treatment options.

The majority of included studies were retrospective case series, which do not provide comparative data and are affected by inherent biases in study design. Generally small sample sizes, the diversity of indications and outcomes reporting, and the high possibility of duplicate reporting require that the findings of this review be interpreted conservatively.

Safety

There were no safety data reported in the identified literature for the most commonly utilised comparator, standard medical management. This resulted in safety being evaluated for SNS in isolation, based on the non-comparative data available from the treatment arms of RCTs, case series and case reports.

The simultaneous evolution of the SNS device (primarily the development of tined leads) and surgical procedure (the change from abdominal to buttock placement of the generator) made it difficult to separate the effects of each of these changes on the safety profile of the procedure overall. Safety artefacts from each of the changes may impact on the other; however, this level of detail could not be extracted from the available evidence. There may also be a learning curve associated with the surgical technique that repeats to a degree each time the procedure is modified. It may be some time before the accumulation of expertise in the new surgical technique is evident in the literature, along with the full impact of the modified device.

Effectiveness

The reporting of effectiveness outcomes was compromised by the lack of uniform outcome measurements. Definitions of 'response' across the studies were not standardised, and other outcomes were frequently based on subjective patient responses.

There were limited data beyond 3 years follow-up to allow assessment of the durability of the device and procedure beyond this time. The available data suggest that effectiveness of SNS may decline slightly over time in some patients; however, the majority of patients maintained statistically significant benefit from the device at 3 years. The reasons for a decline in effectiveness over time are difficult to elucidate, particularly while the

mechanism of action underlying SNS is yet to be fully understood. Theories to account for late failure of the device include gradual displacement of the leads, the need for continual parameter optimisation and plasticity of the micturition centres.

Further compounding the problems caused by short follow-up times was the fact that the reasons for losses to follow-up were rarely explicitly discussed. This has resulted in a risk of attrition bias across the dataset.

The development of a stricter patient screening algorithm and more definitive and reliable screening techniques may have an additional impact on the overall effectiveness of the SNS procedure that is yet to be fully reflected in the published literature.

Chronic sacral nerve stimulation for urinary indications is an evolving procedure that is thought to be highly effective in certain patient populations. This is supported as far as possible by limited data, but the current methods of SNS may never be fully supported by methodologically rigorous evidence, as the nature of the procedure precludes the undertaking of comprehensive randomised controlled trials.

Conclusions

The systematic literature search of this current review has encompassed a broader set of underlying indications and identified further comparative and case series data that have increased the evidence base for the use of SNS since the completion of Application 1009 in 2000. Further, this update has evaluated the impact on safety and effectiveness associated with recent changes to the device and the surgical procedure for its implantation.

Safety

Adverse events were reported inconsistently across the dataset, with the incidence of complications highly variable among studies. Additionally, comparative safety data were not available, as the RCTs defined standard medical management as the comparator procedure and did not report safety outcomes for these study arms. The safety of chronic SNS for urinary indications was evaluated in a total of 2139 patients overall, although not all outcomes were reported for every patient.

The SNS procedure was not reported to be associated with any mortality and the majority of adverse events experienced were of a relatively minor nature. Device removal was reported at a rate of 9.85 per cent (95% CI: 8.27-11.43) and was undertaken for both technical and clinical reasons.

The need for lead replacement/repositioning was the most frequently reported technical adverse event, occurring in approximately 16 per cent of the 1444 patients for whom this outcome was reported (95% CI: 14.71-18.67). These revisions were often undertaken in an effort to optimise the clinical effectiveness of the SNS device in the absence of definitive evidence of lead migration. Incidence of lead migration across the 1561 patients for whom this outcome was reported was 6.98 per cent (95% CI: 5.72-8.24).

The most commonly reported clinical adverse events were pain of undefined location and severity (occurring at a rate of 22.01 per cent across 901 patients; 95% CI: 22.01-25.49), pain specifically at the IPG site (14.0 per cent across 1434 patients; 95% CI: 12.29-15.89) and infection (5.83 per cent across 1303 patients; 95% CI: 4.56-7.10).

A sub-set of this data reporting safety outcomes specifically for tined leads and buttock placement of the IPG showed lower rates of adverse events compared to the older technique of non-tined leads and abdominal generator placement. This indicates a possible increase in the safety of SNS when utilising the new combination of tined leads and buttock-placed generator.

Further, the safety of SNS for the treatment of urinary indications seems generally comparable to that of SNS for the treatment of faecal incontinence.

Effectiveness

Detrusor overactivity

The best available evidence for the effectiveness of SNS compared to standard medical management in the treatment of detrusor overactivity was provided by two randomised controlled trials employing crossover design. On the basis of this evidence, SNS was

effective in significantly improving a number of key voiding variables, including reducing the number of voids per day, leakage episodes and severity, and degree of urgency. These treatment effects were demonstrated to be dependent on active stimulation. Three studies evaluated the effects of SNS on quality of life. Outcomes were generally positive, but remained equivocal overall.

Evidence from a further 981 patients presented in case series supported the overall effectiveness of SNS for this indication across a variety of voiding variables. The durability of the treatment was evaluated to a maximum follow-up of 60 months; significant improvement was maintained in the majority of patient groups for all outcomes.

Non-obstructive urinary retention

One randomised controlled crossover trial comparing SNS to standard medical management in the treatment of non-obstructive urinary retention showed SNS to be effective. The treatment group displayed a significant reduction in the primary voiding diary variable of volume per catheterisation when compared to the control group. Significant differences in favour of the treatment group in all other measured catheterisation variables were also observed.

Evidence from a further 396 patients presented in case series was consistently supportive of the positive treatment effects demonstrated in the comparative study. Durability was evaluated up to 70 months; treatment effectiveness was maintained.

Painful bladder syndrome

There was no comparative evidence available evaluating the effectiveness of SNS in the treatment of PBS. A range of effectiveness outcomes were reported for 90 patients across six case series. SNS showed significant positive effects in this population, but the small sample size limits definitive conclusions.

Cost-effectiveness

Detrusor overactivity

The Advisory Panel recommended using years of complete dryness as the primary outcome measure, as this matches a major clinical trial. It was not possible to construct a generic outcome measure such as a quality-adjusted life year. Of those who underwent peripheral nerve evaluation, 24.81 per cent were both identified as being suitable for SNS and were likely to achieve complete dryness. However, this outcome measure may underestimate the true effect, as those who pass PNE but do not achieve full dryness may still experience a significant reduction in incontinence. The cost per additional year of complete dryness was estimated to be $9,866 and this was robust to univariate sensitivity analysis. As there is no benchmark against which this value can be judged, it is not possible to determine whether this ICER represents a good use of scarce societal resources.

Non-obstructive urinary retention

As with detrusor overactivity, the outcome measure was selected to match a major clinical trial, with successful results defined as elimination of catheterisation or at least a 50 per cent reduction in catheter volume per catheterisation. Of those who undergo

PNE, 35.31 per cent are expected to achieve these results (and as before, it is arguable that this underestimates the true benefit). The cost per year over the 7 year time horizon of these successful results was estimated to be $7,219. This was robust to sensitivity analysis, although whether this ratio represents good value for money is uncertain.

Painful bladder syndrome

There was no clinical evidence for PBS which could be used in an economic evaluation. Therefore, a costing analysis was undertaken. The incremental cost of PNE and SNS was $11,300 per patient.

Financial implication

The expected number of patients to be treated with PNE (of which a proportion will go on to receive SNS) per year is 200, although the likelihood of 200 in the first year is small due to lack of capacity in the field. If these 200 patients were divided equally amongst the three indications considered (detrusor overactivity, urinary retention and painful bladder syndrome) and the conversion rate from PNE to SNS is assumed to be constant across indications, the economic analysis presented here predicts a total net cost of $2.356 million per annum. This consists of costs incurred by the healthcare system (PNE, SNS and dealing with complications), which sum to $2.600 million, minus the cost reduction associated with reduced use of catheters, pads etc. by the individual ($244,000).

However, expert clinical opinion suggests that the division of patients amongst the indications is not likely to be equal; rather it is anticipated that 90 per cent of patients would present with detrusor overactivity and 10 per cent with urinary retention. Should this be the case, the total net cost would be $2.481 million per annum. This consists of costs incurred by the healthcare system (PNE, SNS and dealing with complications), which sum to $2.600 million, minus the cost reduction associated with reduced use of catheters, pads etc. by the individual ($119,000).

Advice

MSAC has considered the safety, effectiveness and cost-effectiveness of sacral nerve stimulation for urinary indications compared with clinical non-surgical management.

MSAC finds there is evidence for the safety of sacral nerve stimulation in adults with detrusor overactivity, non-obstructive urinary retention and painful bladder syndrome refractory to conservative, non-surgical intervention.

MSAC finds sacral nerve stimulation in adults with detrusor overactivity and non-obstructive urinary retention refractory to conservative, non-surgical intervention is more expensive than, but more effective than clinical non-surgical management.

MSAC finds there is insufficient evidence to assess the effectiveness of sacral nerve stimulation in adults with painful bladder syndrome refractory to conservative, non-surgical intervention.

MSAC recognises the social and quality of life issues associated with these conditions.

MSAC advises that public funding should be supported for the procedure of sacral nerve stimulation in adults with detrusor overactivity and non-obstructive urinary retention refractory to conservative, non-surgical intervention.

MSAC advises that public funding should not be supported for the use of sacral nerve stimulation for treatment of patients with painful bladder syndrome.

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	**Expertise or Affiliation**
Dr Stephen BLAMEY (Chair)	General Surgery
Associate Professor John ATHERTON	Cardiology
Associate Professor Michael CLEARY	Emergency Medicine
Associate Professor Paul CRAFT	Clinical Epidemiology and Oncology
Professor Geoff FARRELL	Gastroenterology
Dr Kwun FONG	Thoracic Medicine
Professor Richard FOX	Medical Oncology
Dr David GILLESPIE	Gastroenterology
Professor Jane HALL	Health Economics
Professor John HORVATH	Chief Medical Officer, Department of Health and Ageing
Associate Professor Terri JACKSON	Health Economics
Professor Brendon KEARNEY	Health Administration and Planning
Associate Professor Frederick KHAFAGI	Nuclear Medicine
Dr Bill GLASSON	Ophthalmologist
Associate Professor Ray KIRK	Health Research
Dr Ewa PIEJKO	General Practice

Dr Ian PROSSER	Haematology
Ms Sheila RIMMER	Consumer Health Issues
Dr Judy SOPER	Radiology
Professor Ken THOMSON	Radiology
Dr Mary TURNER	Australian Health Ministers' Advisory Council Representative
Dr David WOOD	Orthopaedics
Mr Peter WOODLEY	Assistant Secretary, Medical Benefits Schedule (MBS) Policy Development Branch, Department of Health and Ageing

Appendix B Advisory panel

Advisory panel for MSAC Application 1115 Sacral nerve stimulation for urinary indications

Dr Ray Kirk *Chair*	Member of MSAC
Ms Sheila Rimmer *(Second Chair)*	Member of MSAC
Associate Professor Richard Millard *Urologist*	Royal Australasian College of Surgeons nominee
Dr Marcus Carey *Urogynaecologist*	Royal Australian and New Zealand College of Obstetricians and Gynaecologists nominee
Dr John Bolt *Urologist*	ANZ Association of Urological Surgeons nominee
Mr Barry Cahill *Continence Foundation of Australia*	Consumers' Health Forum of Australia nominee

Appendix C Approach to assessment

Search strategy

Table 31 Bibliographic databases searched

Electronic Database	Time period & search limits
AustHealth – including: Australian Medical Index, APAIS Health	January 2000 – 15 January 2008
CINAHL	January 2000 – 15 January 2008
Cochrane Library – including: Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment Database, NHS Economic Evaluation Database	January 2000 – 15 January 2008
EMBASE	January 2000 – 15 January 2008 Limits: humans
Medline	January 2000 – 15 January 2008 Limits: humans
PubMed	January 2000 – 15 January 2008 Limits: humans
Web of Science – Science Citation Index Expanded	January 2000 – 15 January 2008

APAIS – Australian Public Affairs Information Service; ELT – Endovenous laser therapy; NHS – National Health Service

Table 32 Electronic internet databases searched

Electronic Database	Internet address
Centre for Reviews and Dissemination (CRD) / International Network of Agencies for Health Technology Assessment (INAHTA) databases – including: NHS Economic Evaluation Database (NHS EED) / Database of Abstracts of Reviews of Effect (DARE) / Heath Technology Assessment (HTA) Database	http://www.york.ac.uk/inst/crd/
National Health and Medical Research Council (NHMRC) (Australia)	http://www.nhmrc.gov.au
Australian Department of Health and Ageing	http://www.health.gov.au/
Scirus – for Scientific Information Only	http://www.scirus.com
Trip database	http://www.tripdatabase.com
Current Controlled Trials metaRegister	http://controlled-trials.com/
National Library of Medicine Health Services / Technology Assessment Text	http://text.nlm.nih.gov/
National Library of Medicine Locator Plus database	http://locatorplus.gov
New York Academy of Medicine Grey Literature Report	http://www.nyam.org/library/pages/grey_literature_report
US Department of Health and Human Services (reports and publications)	http://www.os.dhhs.gov/

Table 33 Health technology assessment internet sites

Argentina	
•	Institute for Clinical Effectiveness and Health Policy (IECS) http://www.iecs.org.ar/iecs-visor-publicaciones-ing.php
Australia	
•	Adelaide Health Technology Assessment (AHTA) http://www.health.adelaide.edu.au/publichealth/consult/health_techn_assess.html
•	Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) http://www.surgeons.org/asernip-s.htm
•	Centre for Clinical Effectiveness, Monash University http://www.mihsr.monash.org/cce/
•	Health Economics Unit, Monash University http://chpe.buseco.monash.edu.au
•	Medical Services Advisory Committee (MSAC) http://www.msac.gov.au
Austria	
•	Institute of Technology Assessment (ITA) http://www.oeaw.ac.at/ita/e1-3.htm
Brazil	
•	Departamento de Ciência e Tecnologia (DECIT) http://portal.saude.gov.br/portal/saude/area.cfm?id_area=1088
Canada	
•	Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) http://www.aetmis.gouv.qc.ca/site/index.php?home
•	Alberta Heritage Foundation for Medical Research (AHFMR) http://www.ahfmr.ab.ca/publications/
•	Canadian Agency for Drugs and Technologies in Health (CADTH) http://www.cadth.ca/index.php/en/home
•	Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database http://www.mycabot.ca
•	Centre for Health Economics and Policy Analysis (CHEPA), McMaster University http://www.chepa.org
•	Centre for Health Services and Policy Research (CHSPR), University of British Columbia http://www.chspr.ubc.ca
•	Health Utilities Index (HUI) http://www.fhs.mcmaster.ca/hug/index.htm
•	Institute for Clinical and Evaluative Studies (ICES) http://www.ices.on.ca
•	Institute of Health Economics (IHE) http://www.ihe.ca/
•	Ministry of Health and Long-Term Care – Medical Advisory Secretariat http://www.health.gov.on.ca/english/providers/program/mas/mas_mn.html
Denmark	
•	Danish Centre for Evaluation and Health Technology Assessment (DACEHTA) http://www.dacehta.dk
•	Danish Institute for Health Services Research (DSI) http://www.dsi.dk/engelsk.html
Finland	
•	Finnish Office for Health Technology Assessment (FinOHTA) http://finohta.stakes.fi/EN/index.htm
France	
•	Committee for Evaluation and Diffusion of Innovative Techniques (CEDIT) http://cedit.aphp.fr/english/index_present.html
•	French National Authority for Health (HAS) http://www.has-sante.fr
Germany	
•	German Agency for Health Technology Assessment (DAHTA) http://www.dimdi.de/dynamic/en/hta/db/index.htm
Hungary	
•	Unit of Health Economics and Technology Research Assessment (HunHTA) http://hecon.uni-corvinus.hu/corvinus.php?lng=en
The Netherlands	
•	Health Council of the Netherlands Gezondheidsraad http://www.gr.nl/adviezen.php?phpLang=en
New Zealand	
•	New Zealand Health Technology Assessment (NZHTA) http://nzhta.chmeds.ac.nz/
Norway	

• Norwegian Knowledge Centre for the Health Services http://www.kunnskapssenteret.no/
Spain
• Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud Carlos III / Health Technology Assessment Agency (AETS) http://www.isciii.es/htdocs/en/investigacion/Agencia_quees.jsp
• Andalusian Agency for Health Technology Assessment (AETSA) http://www.juntadeandalucia.es/salud/orgdep/aetsa/default.asp?V=EN
• Catalan Agency for Health Technology Assessment (CAHTA) http://www.gencat.net/salut/depsan/units/aatrm/html/en/dir394/index.html
Sweden
• Swedish Council on Technology Assessment in Health Care (SBU) http://www.sbu.se/www/index.asp
• Center for Medical Health Technology Assessment http://www.cmt.liu.se/english/publications
Switzerland
• Swiss Network on Health Technology Assessment (SNHTA) http://www.snhta.ch/
United Kingdom
• National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA) http://www.ncchta.org/
• University of York NHS Centre for Reviews and Dissemination (NHS CRD) http://www.york.ac.uk/inst/crd/
• National Institute for Clinical Excellence (NICE) http://www.nice.org.uk/index.htm
United States
• Agency for Healthcare Research and Quality (AHRQ) http://www.ahrq.gov/clinic/techix.htm
• Harvard School of Public Health – Cost-Utility Analysis Registry http://www.tufts-nemc.org/cearegistry/
• U.S. Blue Cross/ Blue Shield Association Technology Evaluation Centre (TEC) http://www.bcbs.com/betterknowledge/tec/
• Veterans' Affairs Technology Assessment Program (VATAP) http://www.va.gov/vatap/publications.htm
International bodies
• International Continence Society http://www.icsoffice.org

Inclusion criteria

Table 34 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	*Effectiveness:* systematic reviews and clinical studies (including comparative studies and case series) will be included. Non-systematic reviews, case reports, letters, editorials, animal, in-vitro and laboratory studies will be excluded. *Safety:* systematic reviews and clinical studies including randomised and non-randomised comparative studies, case series and case reports will be included. Non-systematic reviews, letters, editorials, animal, in-vitro and laboratory studies will be excluded.
Patient	Male or female patients >18 years diagnosed with refractory detrusor overactivity, non-obstructive urinary retention or painful bladder syndrome
Intervention	Chronic sacral nerve stimulation
Comparator	*Detrusor overactivity:* Standard non-surgical management, bladder denervation, bladder reconstruction, urinary diversion (+/- cystectomy) or augmentation cystoplasty *Non-obstructive retention:* Clean intermittent self-catheterisation, indwelling catheter or urinary diversion (+/- cystectomy) *Painful bladder syndrome:* Standard non-surgical management, bladder denervation, bladder reconstruction, urinary diversion (+/- cystectomy), augmentation cystoplasty, hydrostatic dilation or other bladder instillation therapies
Outcome	Effectiveness: *All indications:* cure/response rate, patient related outcomes, parameter adjustments *Detrusor overactivity:* number of leakages/24 hours, severity of leakages, pad use/24 hours, pad weight *Non-obstructive retention:* volume/catheterisation, catheterisations/24 hours, voids/24 hours, volume/void *Painful bladder syndrome* voids/24 hours, volume/void Safety: *All indications:* complication/adverse event rate, revision surgery/explant rate, mortality
Language	Non-English language articles will be excluded unless they appear to provide a higher level of evidence than English language articles.

Search terms

#1	Search: detrusor overactivity Field: text word
#2	Search: urge incontinence Field: text word
#3	Search: urinary incontinence Field: text word
#4	Search: overactive bladder Field: text word
#5	Search: urinary retention Field: text word
#6	Search: Fowler's Syndrome Field: text word
#7	Search: interstitial cystitis Field: text word
#8	Search: painful bladder syndrome Field: text word
#9	Search: chronic pelvic pain
#10	Search: #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
#11	Search: sacral nerve stimulation Field: text word
#12	Search: sacral anterior root stimulation Field: text word
#13	Search: SNS Field: text word
#14	Search: InterStim Field: text word
#15	Search: peripheral nerve evaluation Field: text word
#16	Search neurostimulation Field: text word
#17	Search: neuromodulation Field: text word
#18	Search: functional electrical stimulation Field: text word
#19	Search: FES Field: text word
#20	Search: #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#21	Search: #10 AND #20
	Limits: humans, published 2000 onwards

Appendix D Studies excluded from the review

After full-text evaluation, the following studies were excluded from further consideration in this review for the reasons listed below.

Abstract / conference proceeding

Anoia EJ, Foster RT et al (2006). Long-term satisfaction after sacral neuromodulation for refractory urge incontinence. *Journal of Urology*, 175(4): 289.

Bade JJ & Smans AJ (2006). Long-term efficacy of sacral neuromodulation (interstim) in patients with refractory interstitial cystitis (IC) shows tendency to decrease. *Journal of Urology*, 175(4): 98.

Bade JJ, van Koeverden G, Smans AJ (2005). Minimally invasive technique with tined lead increased screening success rate for sacral neuromodulation in patients with refractory interstitial cystitis (IC). *European Urology Supplements*, 4(3): 143.

Braun PM, Seif C et al (2002). A new approach to chronic, bilateral, sacral neuromodulation in patients with bladder dysfunction. *Urologe A*, 41(1): 44-47.

Caraballo R, Bologna RA et al (2001). Sacral nerve stimulation as a treatment for urge incontinence and associated pelvic floor disorders at a pelvic floor center: a follow-up study. *Urology*, 57(Suppl 6A): 121.

Comiter C (2004). Sacral neuromodulation for the treatment of interstitial cystitis. *Journal of Urology*, 171(4): 94-95.

DasGupta R, Apostolidis A, Fowler CJ (2003). Urodynamic findings after successful sacral nerve stimulation for urinary retention. *Journal of Urology*, 169(4): 321.

Kavia RBC, Mishra V et al (2005). Sacral neuromodulation for women with urinary retention: long term results for the first 30 patients. *BJU International*, 95(Suppl 5): 69-70.

Oerlemans D, Van Voskuilen A et al (2007). Is on-demand sacral nerve stimulation in patients with urge incontinence or urgency frequency a feasible therapy regime? *European Urology Supplements*, 6(2): 143.

Peters KM, Bennett RC et al (2007). Changes in symptoms and urinary HB-EGF, EGF, and antiproliferative factor during chronic neuromodulation for refractory interstitial cystitis. *Journal of Urology*, 177(4): 40-41.

Romero AA, Webster GD, Amundsen CL (2004). Sacral neuromodulation for intractable urge incontinence in women: The impact of patient age on outcome. *Journal of Urology*, 171(4): 325.

Rueff SA, Macdiarmid SA, Wiygul RD (2003). Efficacy of sacral nerve stimulation in combination with behavioral and physical therapy in the treatment of chronic pelvic pain and voiding dysfunction. *Journal of Urology*, 169(4): 68.

van Voskuilen AC, Weil EHJ et al (2005). Ten years' experience in neuromodulation in Maastricht. *Neuromodulation*, 8(3): 183-185.

van Voskuilen AC, Weil EHJ, Van Kerrebroeck PEVA (2005). Tined lead implantation: Results of the first 37 implants in Maastricht. *Neuromodulation*, 8(3): 182-183.

Vaze AA, Rackley RR et al (2005). Neuromodulation for interstitial cystitis. *Journal of Urology*, 173(4): 85.

Wefer B, Seif C et al (2007). Sacral neuromodulation for chronic urinary retention - Contemporary results of a single centre. *European Urology Supplements*, 6(2): 141.

Case report (efficacy outcomes only)

Zermann DH, Weirich T et al (2000). Sacral nerve stimulation for pain relief in interstitial cystitis. *Urologia Internationalis*, 65(2): 120-121.

Comparator not MBS listed

Peters KM, Feber KM, Bennett RC (2007). A prospective, single-blind, randomized crossover trial of sacral vs pudendal nerve stimulation for interstitial cystitis. *BJU International*, 100(4): 835-839.

Duplicate reporting

Aboseif S, Tamaddon K et al (2002). Sacral neuromodulation in functional urinary retention: an effective way to restore voiding. *BJU International*, 90(7): 662-665.

Edlund C, Dijkema HE et al (2004). Sacral nerve stimulation for refractory urge symptoms in elderly patients. *Scandinavian Journal of Urology & Nephrology*, 38(2): 131-135.

Hijaz A and Vasavada S (2005). Complications and troubleshooting of sacral neuromodulation therapy. *Urologic Clinics of North America*, 32(1): 65-69.

English abstract only

Ruffion A, N'Goi C et al (2003). Two indications for bilateral neuromodulation. *Progres en Urologie*, 13(6): 1394-1396.

Inappropriate outcomes reported

Pauls RN, Marinkovic SP et al (2007). Effects of sacral neuromodulation on female sexual function. *International Urogynecology Journal*, 18(4): 391-395.

Mixed outcomes only reported

Scheepens WA, van Koeveringe GA et al (2003). Urodynamic results of sacral neuromodulation correlate with subjective improvement in patients with an overactive bladder. *European Urology*, 43(3): 282-287.

Outcomes from PNE only reported

Borawski KM, Foster RT et al (2007). Predicting implantation with a neuromodulator using two different test stimulation techniques: A prospective randomized study in urge incontinent women. *Neurourology & Urodynamics*, 26(1): 14-18.

Carey M, Fynes M et al (2001). Sacral nerve root stimulation for lower urinary tract dysfunction: overcoming the problem of lead migration. *BJU International*, 87(1): 15-18.

Foster RT, Anoia EJ et al (2007). In patients undergoing neuromodulation for intractable urge incontinence a reduction in 24-hr pad weight after the initial test stimulation best predicts long term patient satisfaction. *Neurourology and Urodynamics*, 26(2): 213-217.

Kessler TM, Madersbacher H, Kiss G (2005). Prolonged sacral neuromodulation testing using permanent leads: a more reliable patient selection method? *European Urology*, 47(5): 660-665.

Maher CF, Carey MP et al (2001). Percutaneous sacral nerve root neuromodulation for intractable interstitial cystitis. *Journal of Urology*, 165(3): 884-886.

Rosenblum N, Eilber KS, Raz S (2003). Herpes zoster following sacral nerve stimulation for overactive bladder. *Journal of Urology*, 169(2): 619-620.

Scheepens WA, de Bie RA et al (2002). Unilateral versus bilateral sacral neuromodulation in patients with chronic voiding dysfunction. *Journal of Urology*, 168(5): 2046-2050.

Sherman ND, Jamison MG et al (2005). Sacral neuromodulation for the treatment of refractory urinary urge incontinence after stress incontinence surgery. *American Journal of Obstetrics and Gynecology*, 193(6): 2083-2087.

Swinn MJ, Kitchen ND et al (2000). Sacral neuromodulation for women with Fowler's syndrome. *European Urology*, 38(4): 439-443.

Whitmore KE, Payne CK et al (2003). Sacral neuromodulation in patients with interstitial cystitis: a multicenter clinical trial. *International Urogynecology Journal*, 14(5): 305-308.

Urodynamic outcomes only reported

Everaert K, De Muynck M et al (2003). Urinary retention after hysterectomy for benign disease: extended diagnostic evaluation and treatment with sacral nerve stimulation. *BJU International*, 91(6): 497-501.

Groen J, Ruud Bosch JL, van Mastrigt R (2006). Sacral neuromodulation in women with idiopathic detrusor overactivity incontinence: decreased overactivity but unchanged bladder contraction strength and urethral resistance during voiding. *Journal of Urology*, 175(3): 1005-1009

Groen J, van Mastrigt R, Bosch JL (2001). Computerized assessment of detrusor instability in patients treated with sacral neuromodulation. *Journal of Urology*, 165(1): 169-173.

Review / discussion – no clinical outcomes reported

Abrams P, Blaivas JG et al (2003). The role of neuromodulation in the management of urinary urge incontinence. *BJU International*, 91(4): 355-359.

Antolak J (2003). Re: Sacral neuromodulation for the symptomatic treatment of refractory interstitial cystitis: A prospective study (multiple letters). *Journal of Urology*, 170(5): 1956.

Costa JA and Kreder KJ (2000). Spinal cord neuromodulation for voiding dysfunction. *Clinical Obstetrics and Gynecology*, 43(3): 676-688.

Junemann K-P (2004). Does the one- or two-stage implantation technique for sacral neuromodulation more effectively relieve LUTS? *Nature Clinical Practice Urology,* 1(1): 20-21.

Pathak AS and Aboseif SR (2005). Overactive bladder: drug therapy versus nerve stimulation. *Nature Clinical Practice Urology*, 2(7): 310-311.

Ruffion A, Dembele D et al (2003). Sacral root neuromodulation for the treatment of urinary incontinence reported to detrusor hyperactivity. *Neurochirurgie*, 49(2-3): 377-382.

Starkman JS, Wolter CE et al (2007). Management of refractory urinary urge incontinence following urogynecological surgery with sacral neuromodulation. *Neurourology and Urodynamics*, 26(1): 36.

Van Kerrebroeck P (2006). Re: Sutherland SE, Lavers A, Carlson A. Holtz C, Kesha J, Siegel SW. 2006. Sacral nerve stimulation for voiding dysfunction: One institution's 11-year experience. *Neurourology & Urodynamics*, 26:19-28;

Wein A (2005) J. Long-term results of sacral neuromodulation for women with urinary retention. *Journal of Urology*, 174(3): 1008.

Zermann D-H, Ishigooka M, Schubert J (2001). Percutaneous sacral third nerve root neurostimulation improves symptoms and normalizes urinary HB-EGF levels and antiproliferative activity in patients with interstitial cystitis. *Urology*, 57(1): 207.

Appendix E Studies included in the review

Table 35 Summary of studies included for safety & effectiveness (urinary indications)

Effectiveness				Safety			
Study	**DO**	**UR**	**PBS**	**Study**	**DO**	**UR**	**PBS**
Comparative studies							
Everaert 2004 (1- v. 2-stage)	✓	✓		Everaert 2004 (1- v. 2-stage)	✓	✓	
Hassouna 2000 (SNS v. SMM)	✓			Hassouna 2000 (SNS v. SMM)	✓		
Jonas 2001 (SNS v. SMM)		✓		Jonas 2001 (SNS v. SMM)		✓	
Weil 2000 (SNS v. SMM)	✓			Weil 2000 (SNS v. SMM)	✓		
Das 2004 (SNS v. SMM) QoL	✓	✓					
Case series							
Aboseif 2002	✓	✓		Aboseif 2002	✓	✓	✓
Amundsen 2002	✓			Aboseif 2007	✓	✓	✓
Amundsen 2005	✓			Amundsen 2002	✓		
Bosch 2000	✓			Amundsen 2005	✓		
Cappellano 2001	✓			Bosch 2000	✓		
Comiter 2003			✓	Comiter 2003			✓
DasGupta 2004		✓		DasGupta 2004		✓	
Datta 2008		✓		Datta 2008		✓	
De Ridder 2007		✓		De Ridder 2007		✓	
Edlund 2000	✓			Deng 2006	…	…	…
Elhilali 2005	✓	✓	✓	Diokno 2003 (CR)	✓		✓
Groenendijk 2007	✓	✓		Edlund 2000	✓		
Hedlund 2002	✓			Elhilali 2005	✓	✓	✓
Janknegt 2001	✓			Everaert 2000	✓	✓	✓
Kessler 2007	✓	✓	✓	Gaynor-Krupnick 2006	✓	✓	
Latini 2006	✓			Groenendijk 2007	✓	✓	
Peters 2003			✓	Hedlund 2002	✓		
Peters 2004			✓	Hijaz 2006	✓		
Roupret 2004	✓			Janknegt 2001	✓		
Scheepens 2002	✓	✓		Kessler 2005 (CR)	✓		
Siegel 2000	✓	✓		Kessler 2007	✓	✓	✓
Spinelli 2001	✓	✓		Latini 2006	✓		
Spinelli 2003a	✓	✓		Nold 2007 (CR)	✓		
Spinelli 2005	✓	✓		Peters 2003			✓
Starkman 2007	✓			Roupret 2004	✓		
Steinberg 2007			✓	Scheepens 2001	✓	✓	✓
Sutherland 2007	✓	✓		Scheepens 2002	✓	✓	
Van Kerrebroeck 2007	✓	✓		Selmer 2006 (CR)	✓		
Van Voskuilen 2006	✓	✓		Siegel 2000	✓	✓	
Van Voskuilen 2007	✓	✓		Spinelli 2001	✓	✓	
				Spinelli 2003a	✓	✓	
				Spinelli 2003b	✓	✓	✓
				Spinelli 2005	✓	✓	
				Starkman 2007	✓		
				Sutherland 2007	✓	✓	
DO detrusor overactivity; UR urinary retention; PBS painful bladder syndrome; SNS sacral nerve stimulation; SMM standard medical management; CR case report; QoL quality of life; … not reported				Van Kerrebroeck 2007	✓	✓	
				Van Voskuilen 2006	✓	✓	
				Van Voskuilen 2007	✓	✓	
				Washington 2007	✓	✓	

Studies included for safety

Urinary indications

Comparative studies

Everaert K, Kerckhaert W et al (2004). A prospective randomized trial comparing the 1-stage with the 2-stage implantation of a pulse generator in patients with pelvic floor dysfunction selected for sacral nerve stimulation. *European Urology* 45(5): 649-654.

Hassouna MM, Siegel SW et al (2000). Sacral neuromodulation in the treatment of urgency-frequency symptoms: A multicenter study on efficacy and safety. *Journal of Urology* 163(6): 1849-1854.

Jonas U, Fowler CJ et al (2001). Efficacy of sacral nerve stimulation for urinary retention: results 18 months after implantation. *Journal of Urology* 165(1): 15-19.

Weil EH, Ruiz-Cerda JL et al (2000). Sacral root neuromodulation in the treatment of refractory urinary urge incontinence: a prospective randomized clinical trial. *European Urology* 37(2): 161-171.

Case series

Aboseif S, Tamaddon K et al (2002). Sacral neuromodulation as an effective treatment for refractory pelvic floor dysfunction. *Urology* 60(1): 52-56.

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Comiter CV (2003). Sacral neuromodulation for the symptomatic treatment of refractory interstitial cystitis: a prospective study. *Journal of Urology* 169(4): 1369-1373.

DasGupta R, Wiseman OJ et al (2004). Long-term results of sacral neuromodulation for women with urinary retention. *BJU International* 94(3): 335-337.

Datta SN, Chaliha C et al (2008). Sacral neurostimulation for urinary retention: 10-Year experience from one UK centre. *BJU International.* 101(2): 192-196.

De Ridder D, Ost D & Bruyninckx F (2007). The presence of Fowler's syndrome predicts successful long-term outcome of sacral nerve stimulation in women with urinary retention. *European Urology* 51(1): 229-233.

Deng DY, Gulati M et al (2006). Failure of sacral nerve stimulation due to migration of tined lead. *Journal of Urology* 175(6): 2182-2185.

Diokno AC, Burgess S & Mulholland T (2003). Complication of the sacral neuromodulator: Lead avulsion and wire disruption. *Journal of Urology* 169(1): 283-284.

Edlund C, Hellstrom M et al (2000). First Scandinavian experience of electrical sacral nerve stimulation in the treatment of the overactive bladder. *Scandinavian Journal of Urology & Nephrology* 34(6): 366-376.

Elhilali MM, Khaled SM et al (2005). Sacral neuromodulation: long-term experience of one center. *Urology* 65(6): 1114-1117.

Everaert K, De Ridder D et al (2000). Patient satisfaction and complications following sacral nerve stimulation for urinary retention, urge incontinence and perineal pain: a multicenter evaluation. *International Urogynecology Journal* 11(4): 231-235.

Gaynor-Krupnick DM, Dwyer NT et al (2006). Evaluation and management of malfunctioning sacral neuromodulator. *Urology* 67(2): 246-249.

Groenendijk PM, Nijeholt AABL et al (2007). Five-year follow-up after sacral neuromodulation: Single center experience. *Neuromodulation* 10(4): 363-368.

Hedlund H, Schultz A et al (2002). Sacral neuromodulation in Norway: clinical experience of the first three years. *Scandinavian Journal of Urology & Nephrology Supplementum*(210): 87-95.

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Kessler TM, Madersbacher H & Kiss G (2005). Bilateral migration of sacral neuromodulation tined leads in a thin patient. *Journal of Urology* 173(1): 153-154.

Kessler TM, Buchser E et al (2007). Sacral neuromodulation for refractory lower urinary tract dysfunction: results of a nationwide registry in Switzerland. *European Urology* 51(5): 1357-1363.

Latini JM, Alipour M & Kreder KJ, Jr. (2006). Efficacy of sacral neuromodulation for symptomatic treatment of refractory urinary urge incontinence. *Urology* 67(3): 550-553.

Nold CJ & McLennan MT (2007). Spontaneous extrusion of sacral nerve implant secondary to massive weight loss. *International Urogynecology Journal* 18(1): 105-107.

Peters KM, Carey JM & Konstandt DB (2003). Sacral neuromodulation for the treatment of refractory interstitial cystitis: outcomes based on technique. *International Urogynecology Journal* 14(4): 223-228.

Roupret M, Chartier-Kastler E et al (2004). Sacral neuromodulation for refractory detrusor overactivity in women with an artificial urinary sphincter. *Journal of Urology* 172(1): 236-239.

Scheepens WA, Weil EHJ et al (2001). Buttock placement of the implantable pulse generator: A new implantation technique for sacral neuromodulation - A multicenter study. *European Urology* 40(4): 434-438.

Scheepens WA, van Koeveringe GA et al (2002). Long-term efficacy and safety results of the two-stage implantation technique in sacral neuromodulation. *BJU International* 90(9): 840-845.

Selmer C & Toglia M (2006). A case of Clostridium difficile colitis after antibiotic prophylaxis for neurostimulator implantation. *Journal of Pelvic Medicine and Surgery* 12(1): 41-43.

Siegel SW, Catanzaro F et al (2000). Long-term results of a multicenter study on sacral nerve stimulation for treatment of urinary urge incontinence, urgency-frequency, and retention. *Urology* 56(6:Suppl 1): Suppl-91.

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Spinelli M, Giardiello G et al (2003a). New sacral neuromodulation lead for percutaneous implantation using local anesthesia: description and first experience. *Journal of Urology* 170(5): 1905-1907.

Spinelli M, Giardiello G et al (2003). New percutaneous technique of sacral nerve stimulation has high initial success rate: Preliminary results. *European Urology* 43(1): 70-74.

Spinelli M, Weil E et al (2005). New tined lead electrode in sacral neuromodulation: experience from a multicentre European study. *World Journal of Urology* 23(3): 225-229.

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Sutherland SE, Lavers A et al (2007). Sacral nerve stimulation for voiding dysfunction: One institution's 11-year experience. *Neurourology & Urodynamics* 26(1): 19-28.

van Kerrebroeck PE, van Voskuilen AC et al (2007). Results of sacral neuromodulation therapy for urinary voiding dysfunction: outcomes of a prospective, worldwide clinical study. *Journal of Urology* 178(5): 2029-2034.

van Voskuilen AC, Oerlemans DJ et al (2006). Long term results of neuromodulation by sacral nerve stimulation for lower urinary tract symptoms: a retrospective single center study. *European Urology* 49(2): 366-372.

van Voskuilen AC, Oerlemans DJ et al (2007). Medium-term experience of sacral neuromodulation by tined lead implantation. *BJU International* 99(1): 107-110.

Washington BB & Hines BJ (2007). Implant infection after two-stage sacral nerve stimulator placement. *International Urogynecology Journal* 18(12): 1477-1480.

Faecal incontinence

Case series

Altomare DF, Rinaldi M et al (2004a). Permanent sacral nerve modulation for fecal incontinence and associated urinary disturbances. *International Journal of Colorectal Disease*, 19(3): 203-209.

Conaghan P & Farouk R (2005). Sacral nerve stimulation can be successful in patients with ultrasound evidence of external anal sphincter disruption. *Diseases of the Colon & Rectum*, 48(8): 1610-1614.

Faucheron JL, Bost R et al (2006). Sacral neuromodulation in the treatment of severe anal incontinence. Forty consecutive cases treated in one institution. *Gastroenterologie Clinique et Biologique*, 30(5): 669-672.

Ganio E, Ratto C et al (2001). Neuromodulation for fecal incontinence: outcome in 16 patients with definitive implant. The initial Italian Sacral Neurostimulation Group (GINS) experience. *Diseases of the Colon & Rectum*, 44(7), 965-970.

Ganio E, Luc AR et al (2002). Sacral nerve modulation for fecal incontinence: Functional results and assessment of the quality of life. [Accessed April 2008] http://www.colorep.it/Rivista%20CEC/sacral_nerve_modulation_for_feca.htm.

Hetzer FH, Bieler A et al (2006a). Outcome and cost analysis of sacral nerve stimulation for faecal incontinence. *British Journal of Surgery*, 93(11): 1411-1417.

Hetzer FH, Hahnloser D et al (2006b). Video-assisted sacral nerve stimulation. *Techniques in Coloproctology*, 10(2): 121-123.

Hetzer FH, Hahnloser D et al (2007). Quality of life and morbidity after permanent sacral nerve stimulation for fecal incontinence. *Archives of Surgery*, 142(1): 8-13.

Holzer B, Rosen HR et al (2007). Sacral nerve stimulation for neurogenic faecal incontinence. *British Journal of Surgery*, 94(6): 749-753.

Jarrett ME, Varma JS et al (2004). Sacral nerve stimulation for faecal incontinence in the UK. *British Journal of Surgery*, 91(6): 755-761.

Jarrett ME, Matzel KE et al (2005a). Sacral nerve stimulation for fecal incontinence following surgery for rectal prolapse repair: a multicenter study. *Diseases of the Colon & Rectum*, 48(6): 1243-1248.

Jarrett ME, Matzel KE et al (2005b). Sacral nerve stimulation for faecal incontinence in patients with previous partial spinal injury including disc prolapse. *British Journal of Surgery*, 92(6): 734-739.

Kenefick NJ (2006). Sacral nerve neuromodulation for the treatment of lower bowel motility disorders. *Annals of the Royal College of Surgeons of England*, 88(7): 617-623.

Leroi AM, Michot F et al (2001). Effect of sacral nerve stimulation in patients with fecal and urinary incontinence. *Diseases of the Colon & Rectum*, 44(6): 779-789.

Leroi AM, Parc Y et al (2005). Efficacy of sacral nerve stimulation for fecal incontinence: results of a multicenter double-blind crossover study. *Annals of Surgery*, 242(5): 662-669.

Malouf AJ, Vaizey CJ et al (2000). Permanent sacral nerve stimulation for fecal incontinence. *Annals of Surgery*, 232(1): 143-148.

Matzel KE, Stadelmaier U et al (2001). Chronic sacral spinal nerve stimulation for fecal incontinence: Long-term results with foramen and cuff electrodes. *Diseases of the Colon & Rectum*, 44(1): 59-66.

Matzel KE, Kamm MA et al (2004). Sacral spinal nerve stimulation for faecal incontinence: multicentre study. *The Lancet*, 363(9417): 1270-1276.

Melenhorst J, Koch SM et al (2007). Sacral neuromodulation in patients with faecal incontinence: results of the first 100 permanent implantations. *Colorectal Disease*, 9(8): 725-730.

Michelsen HB, Buntzen S et al (2006). Rectal volume tolerability and anal pressures in patients with fecal incontinence treated with sacral nerve stimulation. *Diseases of the Colon & Rectum*, 49(7): 1039-1044.

Rasmussen OO, Buntzen S et al (2004). Sacral nerve stimulation in fecal incontinence. *Diseases of the Colon & Rectum*, 47(7): 1158-1163.

Ratto C, Morelli U et al (2003). Minimally invasive sacral neuromodulation implant technique: modifications to the conventional procedure. *Diseases of the Colon & Rectum,* 46(3): 414-417.

Rosen HR, Urbarz C et al (2001). Sacral nerve stimulation as a treatment for fecal incontinence. *Gastroenterology,* 121(3): 536-541.

Uludag O, Koch SMP et al (2004). Sacral neuromodulation in patients with fecal incontinence: A single-center study. *Diseases of the Colon & Rectum*, 47(8): 1350-1357.

Studies included for effectiveness

Comparative studies

Das AK, Carlson AM et al (2004). Improvement in depression and health-related quality of life after sacral nerve stimulation therapy for treatment of voiding dysfunction. *Urology* 64(1): 62-68.

Everaert K, Kerckhaert W et al (2004). A prospective randomized trial comparing the 1-stage with the 2-stage implantation of a pulse generator in patients with pelvic floor dysfunction selected for sacral nerve stimulation. *European Urology* 45(5): 649-654.

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Latini JM, Alipour M & Kreder KJ, Jr. (2006). Efficacy of sacral neuromodulation for symptomatic treatment of refractory urinary urge incontinence. *Urology* 67(3): 550-553.

Peters KM, Carey JM & Konstandt DB (2003). Sacral neuromodulation for the treatment of refractory interstitial cystitis: outcomes based on technique. *International Urogynecology Journal* 14(4): 223-228.

Peters KM & Konstandt D (2004). Sacral neuromodulation decreases narcotic requirements in refractory interstitial cystitis. *BJU International* 93(6): 777-779.

Roupret M, Chartier-Kastler E et al (2004). Sacral neuromodulation for refractory detrusor overactivity in women with an artificial urinary sphincter. *Journal of Urology* 172(1): 236-239.

Scheepens WA, van Koeveringe GA et al (2002). Long-term efficacy and safety results of the two-stage implantation technique in sacral neuromodulation. *BJU International* 90(9): 840-845.

Siegel SW, Catanzaro F et al (2000). Long-term results of a multicenter study on sacral nerve stimulation for treatment of urinary urge incontinence, urgency-frequency, and retention. *Urology* 56(6:Suppl 1): Suppl-91.

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Spinelli M, Giardiello G et al (2003a). New sacral neuromodulation lead for percutaneous implantation using local anesthesia: description and first experience. *Journal of Urology* 170(5): 1905-1907.

Spinelli M, Weil E et al (2005). New tined lead electrode in sacral neuromodulation: experience from a multicentre European study. *World Journal of Urology* 23(3): 225-229.

Starkman JS, Wolter CE et al (2007). Management of refractory urinary urge incontinence following urogynecological surgery with sacral neuromodulation. *Neurourology & Urodynamics* 26(1): 29-35.

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van Voskuilen AC, Oerlemans DJ et al (2007). Medium-term experience of sacral neuromodulation by tined lead implantation. *BJU International* 99(1): 107-110.

Appendix F Clinical trials & health technology assessments

Clinical trials

Completed

Title: InterStim therapy retrospective cost analysis and quality of life
Institution: Southern California Permanente Medical Group, USA
Contact: Sherif Aboseif
Start date: -
Expected completion date: April 2006
Identifier: US NIH clinicaltrials.gov NCT0020031

Title: Performance of the miniaturo™-I system for treatment of overactive bladder
Institution: University Medical Centre Utrecht, THE NETHERLANDS
Contact: Professor J Bosch
Start date: -
Expected completion date: 30/11/2007
Identifier: Current Controlled Trials ISRCTN08364639

Ongoing

Title: Patient registry to study the tined lead used with the InterStim system for urinary control
Institution: Medtronic
Contact: Medtronic Gastroenterology and Urology
Start date: August 2004
Expected completion date: -
Identifier: US NIH clinicaltrials.gov NCT00225966

Recruiting

Title: Performance of the miniaturo™-I system for treatment of urinary urge incontince to improve the number of leaking episodes.
Institution: Royal Melbourne Hospital, Victoria, AUSTRALIA
Contact: Ann Duncan
Start date: 01/08/2007
Expected completion date: -
Identifier: Australian New Zealand Clinical Trials Registry ACTRN12607000390482

Title: A randomised controlled trial comparing the implanted sacral nerve stimulator device with conservative treatment for severe and refractory lower urinary tract symptoms and faecal incontinence.
Institution: Royal Women's Hospital, Victoria, AUSTRALIA
Contact: Dr Marcus Carey/Dr Peta Higgs

Start date: 04/04/2004
Expected completion date: -
Identifier: Australian New Zealand Clinical Trials Registry ACTRN 12605000329662

Title: InterStim prospective database for outcomes research
Institution: William Beaumont Hospital, Michigan, USA
Contact: Dr Kenneth Peters
Start date: -
Expected completion date: April 2029
Identifier: US NIH clinicaltrials.gov NCT00441935

Title: InSite for urinary urgency-frequency
Institution: Multicentre (Medtronic)
Study Director: Darin R Lerew
Start date: October 2007
Expected completion date: November 2015
Identifier: US NIH clinicaltrials.gov NCT00549094

Title: InSite for urinary urge incontinence
Institution: Multicentre (Medtronic)
Study Director: Darin R Lerew
Start date: October 2007
Expected completion date: November 2015
Identifier: US NIH clinicaltrials.gov NCT00547378

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Appendix G Results of assessment: critical appraisal

Table 36 Critical appraisal of case series included for evaluation of effectiveness

Study	Sample size	Indication/s			Outcomes			Statistical methods	Duration of follow-up
	Allocation	DO	UR	PBS	Effect.	Safety	Description		Losses to follow-up
Aboseif 2002	64 …	✓	✓	✓	✓	✓	Objective voiding data Questionnaire resp. (val.)	Tests described Significance level not stated	Mean: 24 (6-36) months Losses: …
Amundsen 2002	12 retrospective	✓			✓	✓	Subjective & objective voiding data	Tests described Significance level stated	Mean: 7.8 (1-16) months Losses: …
Amundsen 2005	55 prospective	✓			✓	✓	Objective voiding data Questionnaire resp. (val.)	Tests described Significance level stated	Mean: 29 (8-48) months Losses: …
Bosch 2000	45 selected px	✓			✓	✓	Objective voiding data	Tests described Significance level stated	Mean: 47.1 (6-96) months Losses: …
Cappellano 2001	113 prospective reg.	✓		✓	✓		Objective voiding data Questionnaire resp. (val.)	Tests not adequately described Significance level not stated	9-18 months Losses: …
Comiter 2003	17 retrospective			✓	✓	✓	Objective voiding data Questionnaire resp. (val.)	Tests described Significance level not stated	Mean: 14 (2-28) months Losses: …
DasGupta 2004	26 retrospective		✓		✓	✓	Objective voiding data	Statistical testing not undertaken	Mean: 37 (2-73) months Losses: …
Datta 2008	60 retrospective		✓		✓	✓	Objective voiding data	Statistical testing not undertaken	Mean: 48 months Losses: Nil
De Ridder 2007	62 consecutive prospective		✓		✓	✓	Objective voiding data	Tests described Significance level not stated	Mean: 43.4 (35.2) months Losses: …
Edlund 2000	30 …	✓			✓	✓	Objective voiding data	Tests described Significance level not stated	Mean: 19.9 (8-39 months) Losses: 1/30
Elhilali 2005	52 retrospective	✓	✓	✓	✓	✓	Subjective voiding data	Statistical testing not undertaken	6.45±0.69 (1.33-13.33) years Losses: 11/52
Groenendijk 2007	22 …	✓	✓		✓	✓	Objective voiding variables	Tests described Significance level not stated	60 months
Hedlund 2002	14 retrospective	✓			✓	✓	Objective voiding variables	Tests described Significance level not stated	Mean: 18 (9-32) months Losses: Nil
Janknegt 2001	96 …	✓			✓	✓	Objective & subjective voiding variables	Tests described Significance level not stated	Mean: 30.8 (12-60) months Losses: …
Kessler 2007	91 consecutive prospective reg.	✓	✓	✓	✓	✓	Objective voiding variables Subjective px responses	Tests described Significance level stated	Range: (5-37) months Losses: …

Table 36 continued… Critical appraisal of case series included for the evaluation of effectiveness

Study	Sample size	Indication/s			Outcomes			Statistical methods	Duration of follow-up
	Allocation	DO	UR	PBS	Effect.	Safety	Description		Losses to follow-up
Latini 2006	41 retrospective	✓			✓	✓	Objective voiding variables	Tests described Significance level not stated	Median: [12] [4.5] months Losses: …
Peters 2003	26 …			✓	✓	✓	Objective voiding data Subjective px responses	Tests described Significance level stated	Mean: 5.6 months Losses: 1/26
Peters 2004	21 retrospective			✓	✓		Objective measures Subjective px responses	Tests described Significance level stated	Mean: 15.4 (7.4-23.1) months Losses: Nil
Roupret 2004	6 …	✓			✓	✓	Objective voiding data	Statistical testing not undertaken	Mean: 30.5 (14-40) months Losses: Nil
Scheepens 2002	12 …	✓	✓		✓	✓	Objective voiding data Subjective px response	Tests described Significance level not stated	Mean: 4.9 [5.2](2.5-7.5) years Losses: Nil
Siegel 2000	112 prospective	✓	✓		✓	✓	Objective voiding data Subjective px response	Tests described Significance level stated	(18-36) months Losses: …
Spinelli 2001	196 prospective & retrospective reg.	✓	✓		✓	✓	Objective voiding data Questionnaire resp. (val.)	Tests described (some generic) Significance level not stated	(24-73) months Losses: at least 32/196
Spinelli 2003a	12 consecutive prospective	✓	✓		✓	✓	Objective voiding data	Statistical testing not undertaken	Mean: 11 (5-19) months Losses: …
Spinelli 2005	41 prospective	✓	✓		✓	✓	Objective voiding data	Tests described Significance level not stated	13.8±7.6 months Losses: …
Starkman 2007	22 retrospective	✓			✓	✓	Objective subjective voiding data	Tests described Significance level not stated	Mean: 7.2 (3-38) months Losses: …
Steinberg 2007	15 retrospective			✓	✓		Objective voiding data Questionnaire resp. (val.)	Tests described Significance level stated	Mean: 14.1 (8-18) months Losses: …
Sutherland 2007	234 retrospective	✓	✓		✓	✓	Objective voiding data Subjective px response	Tests described Significance level stated	Mean: 22 (3-162) months Losses: 130/234
Van Kerrebroeck 2007	163 prospective	✓	✓		✓	✓	Objective voiding data Subjective px response	Tests not described Significance level not stated	49.3±15. (11-60) months Losses: 58/163 at 5 years
Van Voskuilen 2006	175 retrospective	✓	✓		✓	✓	Subjective px response	Tests described Significance level not stated	64.2±38.5 (12-154) months Losses: 26/175
Van Voskuilen 2007	41 …	✓	✓		✓	✓	Objective voiding data	Tests inadequately described Significance level not stated	15.5±7.9 months Losses: 10/41

NOTES: (range) [median] ±standard deviation; reg registry; resp response; val validated; px patient ; … not reported; DO detrusor overactivity; UR urinary retention; PBS painful bladder syndrome

Appendix H Results of assessment: safety

Table 37 Technical adverse events & explantation during SNS for urinary indications: individual study outcomes

Study	Study details			Technical adverse events			Explant
	Patients N=	Leads (patient n=)	Placement (patient n=)	Lead/ electrode migration	Generator malfunction	Lead replacement/ repositioning	Permanent explantation
Aboseif 2002	64	…	…	2	2	4	1
Aboseif 2007	65	T (65)	…	1	1	1	…
Amundsen 2002	12	…	B (12)	…	…	1	…
Amundsen 2005	55	…	…	7	…	2	2
Bosch 2000	45	…	…	9	1	2	0
Comiter 2003	17	…	B (17)	0	0	…	…
DasGupta 2004	26	…	B (9)/ A (17)	1	…	21	…
Datta 2008	60	T (30)/ NT (30)	B (30)/ A (30)	17	…	63	12
De Ridder 2007	62	…	…	…	…	13	9
Deng 2006	235	T (235)	B (235)	5	…	2	…
Diokno 2003 (CR)	2	…	…	3	…	3	…
Edlund 2000	9	…	A (9)	1	3	1	…
Elhilali 2005	41	…	…	…	…	…	5
Everaert 2000	53	NT (53)	A (53)	2	3	15	…
Everaert 2004	42	NT (42)	B (42)	…	…	6	…
Gaynor-Krupnick 2006	82	…	…	5	1	…	…
Groenendijk 2007	22	NT (22)	…	…	…	10	5
Hedlund 2002	14	NT (14)	B (12)/ A (2)	…	…	2	1
Hijaz 2006	161	T (214)	…	1	…	…	17
Janknegt 2001	96	…	…	…	…	…	11
Kessler 2005 (CR)	1	T (1)	B (1)	1	…	0	…
Kessler 2007	91	…	…	2	1	6	12
Latini 2006	41	…	…	…	1	2	2
Nold 2007 (CR)	1	…	B (2)/ A (1)	…	…	…	1
Peters 2003	26	…	B (26)	…	…	0	0

Table 37 continued **Technical adverse events & explantation during SNS for urinary indications: individual study outcomes**

Study	Study details			Technical adverse events			Explant
	Patients N=	Leads (patient n=)	Placement (patient n=)	Lead/ electrode migration	Generator malfunction	Lead replacement/ repositioning	Permanent explantation
Roupret 2004	6	…	…	…	…	…	…
Scheepens 2001	39	NT (39)	B (39)	…	…	…	…
Scheepens 2002	12	…	B (15)	…	…	5	2
Selmer 2006 (CR)	1	…	…	…	…	…	…
Spinelli 2001	196	…	…	6	…	5	8
Spinelli 2003a	12	T (15)	B (12)	0	…	…	…
Spinelli 2003b	22	…	…	4	…	…	1
Spinelli 2005	41	…	…	9	…	3	…
Starkman 2007	22	T: (22)	B (22)	…	…	2	2
Sutherland 2007	104	T (73)/ NT (82)	…	…	…	38	…
Van Kerrebroeck 2007	102	…	B (31)/ A (121)	14	8	26	16
Van Voskuilen 2006	149	…	…	10	…	…	21
Van Voskuilen 2007	31	T (31)	B (31)	1	…	…	…
Washington 2007	37	T (37)	B (37)	…	…	…	5
Weil 2000	42	NT (42)	A (42)	8	…	8	1

NOTES: A abdominal placement, B buttock placement, NT non-tined lead, T tined lead, … not reported; CR case report

Table 38 Clinical adverse events during SNS for urinary indications: individual study outcomes

Study	Clinical adverse events						
	Pain at IPG site	Other pain	Infection	Seroma/ haematoma	Wound complications	Other	Mortality
Aboseif 2002	…	…	3	…	…	…	…
Aboseif 2007	1	…	2	3	1	…	…
Amundsen 2002	2	…	0	0	…	…	…
Amundsen 2005	2	…	1	…	…	…	…
Bosch 2000	2	3	0	1	3	…	…
Comiter 2003	0	…	0	0	…	…	…
DasGupta 2004	6	6	2	…	…	2	…
Datta 2008	19	22	…	…	6	5	0
De Ridder 2007	…	…	…	…	…	…	…
Deng 2006	…	…	…	…	…	…	…
Diokno 2003 (CR)	…	…	…	…	…	…	…
Edlund 2000	…	…	…	…	…	5	…
Elhilali 2005	…	3	2	…	…	…	…
Everaert 2000	18	9	1	…	…	17	…
Everaert 2004	4	2	3	…	…	…	1
Gaynor-Krupnick 2006	1	1	1	1	…	…	…
Groenendijk 2007	2	…	…	…	…	1	1
Hedlund 2002	…	…	…	1	…	2	…
Hijaz 2006	4	…	12	…	…	…	…
Janknegt 2001	…	1	…	…	…	1	…
Kessler 2005 (CR)	…	…	…	…	…	…	…
Kessler 2007	3	…	1		…	3	…
Latini 2006	…	3	7	1	4	2	…
Nold 2007 (CR)	…	…	…	…	…	…	…
Peters 2003	…	…	0	…	…	…	…

Table 38 continued **Clinical adverse events during SNS for urinary indications: individual study outcomes**

Study	Clinical adverse events						
	Pain at IPG site	Other pain	Infection	Seroma/ haematoma	Wound complications	Other	Mortality
Roupret 2004	0	0	0	0	0	0	…
Scheepens 2001	4	…	0	2	…	…	…
Scheepens 2002	2	9	…	…	…	2	…
Selmer 2006 (CR)	…	…	1	…	…	…	…
Spinelli 2001	4	…	…	2	2	5	…
Spinelli 2003a	…	…	…	…	…	…	…
Spinelli 2003b	…	…	0	…	…	…	…
Spinelli 2005	…	…	…	…	…	…	…
Starkman 2007	1	…	2	…	…	1	…
Sutherland 2007	28	1	13	7	…	14	…
Van Kerrebroeck 2007	40	73	14	…	1	113	…
Van Voskuilen 2006	41	64	6	…	…	62	
Van Voskuilen 2007	2	…	…	…	…	1	…
Washington 2007	…	…	5	…	…	…	…
Weil 2000	16	8	…	…	1	6	…

NOTES: … not reported; CR case report; IPG implantable pulse generator

Table 39 Technical adverse events during SNS for faecal incontinence: individual study outcomes

Study	Study details			Technical adverse events			Explant
	Patients N=	Leads (patient n=)	Placement (patient n=)	Lead/ electrode migration	Generator malfunction	Lead replacement/ repositioning	Permanent explantation
Altomare 2004	14	NT (14)	A (8)/ B (6)	2	…	2	…
Conaghan 2005	3	…	B (3)	…	…	1	0
Faucheron 2006	29	T (29)	B (29)	1	1	4	2
Ganio 2001	16	NT (16)	A (16)	0	…	…	…
Ganio 2002	31	NT (31)	A/ B	2	…	…	…
Hetzer 2006a	33	T (33)	…	3	…	6	2
Hetzer 2006b	5	T (5)	B (5)	…	…	…	…
Hetzer 2007	37	NT (5)/ T (39)	B (39)	4	…	7	3
Holzer 2007	29	NT/T	…	5	…	8	…
Jarret 2004a	46	NT (42)/T (4)	A/ B	4	…	3	…
Jarret 2005b	12	NT (12)	A/ B	3	1	5	1
Kenefick 2006	19	…	A (9)/ B (10)	2	…	2	0
Leroi 2001	6	NT (6)	…	1	…	…	…
Leroi 2005	34	T (34)	B (34)	…	…	…	4
Malouf 2000	5	NT (5)	A (5)	1	…	1	…
Matzel 2001	6	NT (6)	A (6)	…	…	3	2
Matzel 2004	34	NT (34)	A/ B	1	…	4	2
Melenhorst 2007	100	…	…	…	…	…	…
Rasmussen 2004	37	NT (37)	…	…	…	…	5
Ratto 2003	10	NT (10)	A/ B	…	…	…	…
Rosen 2001	15	NT (15)	…	2	…	2	4
Uludag 2004	50	…	…	…	…	4	2

NOTES: A abdominal placement; B buttock placement; NT non-tined lead; T tined lead; … not reported

Table 40 Clinical adverse events during SNS for faecal incontinence: individual study outcomes

Study	Clinical adverse events						
	Pain at IPG site	Other pain	Infection	Seroma/ haematoma	Wound complications	Other	Mortality
Altomare 2004	…	…	1	1	…	…	…
Conaghan 2005	1	…	…	…	…	…	…
Faucheron 2006	1	…	2	1	…	…	0
Ganio 2001	1	…	…	…	…	…	…
Ganio 2002	1	…	0	…	…	…	…
Hetzer 2006	1	1	2	1	…	…	…
Hetzer 2006	…	…	0	…	…	…	…
Hetzer 2007	…	4	2	1	…	2	…
Holzer 2007	1	…	2	…	…	1	…
Jarret 2004a	…	3	…	…	…	…	…
Jarret 2005b	2	…	…	…	1	…	…
Kenefick 2006	…	…	0	…	…	…	…
Leroi 2001	…	0	…	…	1	…	…
Leroi 2005	…	3	1	…	…	…	…
Malouf 2000	1	…	…	…	…	…	…
Matzel 2001	1	1	…	…	…	…	…
Matzel 2004a	3	7	1	…	…	….	…
Melenhorst 2007	…	…	…	…	…	…	…
Rasmussen 2004	…	…	2	…	…	…	…
Ratto 2003	…	…	…	1	…	…	…
Rosen 2001	…	…	3	…	…	…	…
Uludag 2004	…	…	2	8	…	….	…

NOTES: … not reported; IPG implantable pulse generator

Table 41 Adverse events with the use of tined and non-tined leads: urinary indications

Indication	Leads	Number of studies	Patients N=	Incidence n=	Rate (%)	95% confidence intervals
Technical adverse events						
Lead/electrode migration	Tined	7	498	11	2.21	-
	Non-tined	3	125	25	20.00	12.99-27.01
Generator malfunction	Tined	1	65	1	1.54	-
	Non-tined	1	33	3	5.66	-1.15-12.47
Lead replacement/repositioning	Tined	5	353	20	5.67	3.26-8.08
	Non-tined	7	173	89	51.45	44.00-58.90
Clinical adverse events						
Pain at IPG site	Tined	5	309	12	3.88	-
	Non-tined	6	198	59	29.80	23.43-36.17
Other pain	Tined	1	30	11	36.67	21.72-51.62
	Non-tined	4	167	30	17.96	12.14-23.78
Infection	Tined	4	285	21	7.37	4.34-10.40
	Non-tined	3	134	4	2.99	-
Seroma/haematoma	Tined	1	65	3	4.62	-
	Non-tined	2	53	3	5.66	0.34-10.98
Wound complications	Tined	2	95	3	3.16	-
	Non-tined	2	72	5	6.94	1.07-12.81
Other	Tined	3	83	4	4.82	-
	Non-tined	5	131	29	22.14	15.03-29.25
Device explant						
Permanent explant	Tined	4	250	29	11.60	7.63-15.57
	Non-tined	4	78	14	17.95	9.43-26.47

NOTES: 95% confidence intervals not calculated if rate <5%; IPG implantable pulse generator

Table 42 Adverse events with the use of tined and non-tined leads: faecal incontinence

Indication	Leads	Number of studies	Patients N=	Incidence n=	Rate (%)	95% confidence intervals
Technical adverse events						
Lead/electrode migration	Tined	2	62	4	6.45	0.34-12.56
	Non-tined	7	118	12	10.17	4.72-15.62
Generator malfunction	Tined	1	29	1	3.45	-
	Non-tined	1	12	1	8.33	-6.00-23.97
Lead replacement/repositioning	Tined	2	62	10	16.13	6.97-25.29
	Non-tined	7	118	19	16.10	9.47-22.73
Clinical adverse events						
Pain at IPG site	Tined	2	62	2	3.13	-
	Non-tined	6	104	9	8.65	3.25-14.05
Other pain	Tined	2	67	4	5.97	0.30-11.64
	Non-tined	2	40	8	20.00	9.34-30.66
Infection	Tined	4	101	5	4.95	-
	Non-tined	6	138	7	5.07	1.41-8.73
Seroma/haematoma	Tined	2	62	2	3.13	-
	Non-tined	3	40	3	7.50	0.48-14.52
Wound complications	Tined	0	0	0	0.00	-
	Non-tined	2	18	2	11.11	-1.78-24.00
Other	Tined	0	0	0	0.00	-
	Non-tined	0	0	0	0.00	-
Device explant						
Permanent explant	Tined	3	96	8	8.33	2.80-13.86
	Non-tined	5	105	14	13.33	6.83-19.83

NOTES: 95% confidence intervals not calculated if rate <5%; IPG implantable pulse generator

Table 43 Adverse events with different generator locations: urinary indications

Indication	Leads	Number of studies	Patients N=	Incidence n=	Rate (%)	95% confidence intervals
Technical adverse events						
Lead/electrode migration	Buttock	6	326	9	2.76	-
	Abdomen	3	104	11	10.58	4.67-16.49
Generator malfunction	Buttock	1	17	0	0.00	-
	Abdomen	2	62	6	9.68	2.32-17.04
Lead replacement/repositioning	Buttock	8	380	31	8.16	5.41-10.91
	Abdomen	3	104	24	23.08	14.98-31.18
Clinical adverse events						
Pain at IPG site	Buttock	8	205	19	9.27	5.30-13.24
	Abdomen	2	95	34	35.79	26.15-45.43
Other pain	Buttock	3	84	22	26.19	16.79-35.59
	Abdomen	2	95	17	17.89	10.18-25.60
Infection	Buttock	7	130	10	7.69	3.11-12.27
	Abdomen	1	53	1	1.89	-
Seroma/haematoma	Buttock	3	68	2	2.94	-
	Abdomen	0	0	-	-	-
Wound complications	Buttock	1	30	2	6.67	-1.07-14.41
	Abdomen	1	42	1	2.38	-
Other	Buttock	4	95	6	6.32	1.43-11.21
	Abdomen	3	104	28	26.92	18.40-35.44
Device explant						
Permanent explant	Buttock	5	127	14	11.02	5.57-16.47
	Abdomen	1	42	1	2.38	-

NOTES: 95% confidence intervals not calculated if rate <5%; IPG implantable pulse generator

Table 44 Adverse events with different generator locations: faecal incontinence

Indication	Leads	Number of studies	Patients N=	Incidence n=	Rate (%)	95% confidence intervals
Technical adverse events						
Lead/electrode migration	Buttock	2	66	5	7.58	1.19-13.97
	Abdomen	1	5	1	20.00	-18.14-58.14
Generator malfunction	Buttock	1	29	1	3.45	-
	Abdomen	0	0	0	0.00	-
Lead replacement/repositioning	Buttock	3	69	12	17.39	8.45-26.33
	Abdomen	2	11	4	36.36	10.08-62.64
Clinical adverse events						
Pain at IPG site	Buttock	2	32	2	6.25	-1.01-13.51
	Abdomen	3	27	3	11.11	0.79-21.43
Other pain	Buttock	2	71	7	9.86	2.93-16.79
	Abdomen	1	6	1	16.66	-13.99-47.31
Infection	Buttock	4	105	5	4.76	-
	Abdomen	0	0	0	0.00	-
Seroma/haematoma	Buttock	2	66	2	3.03	-
	Abdomen	1	16	1	6.25	-4.63-16.86
Wound complications	Buttock	0	0	0	0.00	-
	Abdomen	0	0	0	0.00	-
Other	Buttock	0	0	0	0.00	-
	Abdomen	0	0	0	0.00	-
Device explant						
Permanent explant	Buttock	4	103	9	8.73	3.28-14.18
	Abdomen	1	6	2	33.33	-5.45-72.11

NOTES: 95% confidence intervals not calculated if rate <5%; IPG implantable pulse generator

Appendix I Results of assessment: effectiveness

Table 45 Effectiveness outcomes: detrusor overactivity case series

Study	Follow-up	n= Baseline & with SNS	Effectiveness outcomes – detrusor overactivity						
			Response rate	Voids/day	Volume/ void (mL)	Maximum voided volume (mL)	Incontinent episodes/day	Severity of leakage	Pad use/day
Aboseif 2002	24 months	Baseline: 44	-	17.9	130.1	…	6.4	…	…
		With SNS: 43	80%[a]	8.6	248.4	…	2.0	…	…
		P value	-	sig	…	…	sig	…	<0.05
Admundsen 2002	7.8 months	Baseline: 12	-	11±2	…	…	7±3	4±1[b]	7±3
		With SNS: 12	100% [a]	7±1	…	…	2±1	1±1	2±1
		P value	-	0.16	…	…	0.12	0.07	0.07
Admundsen 2005	29 months	Baseline: 55	-	…	…	…	…	…	…
		With SNS: 55	45%[c] (25/55)	…	…	…	decreased	…	decreased
		P value	-	…	…	…	0.01	…	NS
Bosch 2000	12 months	Baseline: 45	…	13.2 (10.2-15.5)	129 (101-179)	…	7.1 (4.9-9.2)	…	5.4 (3.9-8.6)
		With SNS: 42	…	8.3 (6.6-9.3)	199 (146-233)	…	1.0 (0.0-3.7)	…	1.5 (0.0-3.0)
		P value	…	0.0001	0.0001	…	0.0001	…	0.0001
Cappellano 2001 (detrusor instability)	12 months	Baseline: 47	…	…	…	…	5.8 ±4.2	…	…
		With SNS: 47	…	…	…	…	0.9 ±1.5	…	…
		P value	…	…	…	…	<0.01	…	…
Edlund 2000	8-12 months	Baseline: 9	…	…	…	…	5.9 ±2.2	1.9 ±0.4[d]	3.0 ±2.5
		With SNS: 9	…	…	…	…	2.8 ±1.5	1.6 ±0.4	1.9 ±1.8
		P value	…	…	…	…	0.01	0.02	0.07
Elhilali 2005	NR	Baseline: 28	-	…	…	…	…	…	…
		With SNS: 28	39% (11/28)	…	…	…	…	…	…
		P value	…	…	…	…	…	…	…
Groenendijk 2007 (urge incontinence)	60 months	Baseline: 15	-	…	…	…	11.6	2.2[e]	6.9
		With SNS: 12	80%	…	…	…	3.7	1.9	2.5
		P value	-	…	…	…	0.002	…	0.004
Groenendijk 2007 (urgency-frequency)	60 months	Baseline: 5	-	24	98	…	…	…	…
		With SNS: 2	40%	11	212	…	…	…	…
		P value	-	…	…	…	…	…	…
Hedlund 2002	12 months	Baseline: 13	-	10.0 ±1.1	195 ±25	…	…	579 ±176[f]	8.3 ±1.3
		With SNS: 9	100% [a]	8.0 ±0.6	255 ±27	…	…	16 ±8	1.3 ±0.4
		P value	-	NS	<0.05	…	…	<0.01	<0.01
Janknegt 2001	30.8 months	Baseline: 96	-	13.2 ±6.8	149 ±99	354 ±198	…	2.0 ±0.6[d]	7.1 ±5.1
		With SNS: 89	62%	9.2 ±4.5	200 ±100	392 ±186	…	1.7 ±06	2.9 ±3.8
		P value	-	<0.0001	<0.0001	0.02	…	<0.0001	<0.0001

Table 45 continued… Effectiveness outcomes: detrusor overactivity case series

Study	Follow-up	n= Baseline & With SNS	Effectiveness outcomes - detrusor overactivity *continued...*						
			Response rate	Voids/day	Volume/ void (mL)	Maximum voided volume (mL)	Incontinent episodes/day	Severity of leakage	Pad use/day
Kessler 2007	24 months (median)	Baseline: 71	…	10 (5-13)	…	…	5 (2-10)	…	4 (2-5)
		With SNS: 71	…	6 (4-8)	…	…	0 (0-2)	…	1 (0-3)
		P value	…	0.0005	…	…	<0.0001	…	<0.0001
Latini 2006	4.5-12 months	Baseline: 41	-	…	…	…	8.8 ±6.1	…	4.7 ±2.8
		With SNS: 41	90% [a]	…	…	…	2.3 ±3.4	…	0.8 ±1.1
		P value	-	…	…	…	0.0001	…	<0.0001
RouBaselinet 2004	12 months	Baseline: 6	-	17 (12-23)	121.7 (90-170)	…	14.7 (8.5-17)	…	…
		With SNS: 6	17% [c] (1/6)	8 (4-12)	180 (120-225)	…	6 (4-10)	…	…
		P value	-	…	…	…	…	…	…
Scheepens 2002	4.9 years	Baseline: 7	…	12.9 ±5.8	99.1 ±62.5	168.6 ±191.9	9.0 ±4.3	1.8 ±0.3 [e]	5.0 ±2.4
		With SNS: 7	…	7.9 ±2.2	313.0 ±121.4	617.1 ±211.5	3.2 ±3.4	1.3 ±0.3	1.0 ±1.3
		P value	…	0.05	0.004	0.013	0.079	0.041	0.003
Siegel 2000 (urge incontinence)	18-36 months	Baseline: 41	…	…	…	…	11.6 ±6.6	3.6 ±4.0 [b]	6.7 ±4.6
		With SNS: 41	…	…	…	…	5.0 ±6.1	1.3 ±3.5	3.4 ±4.9
		P value	…	…	…	…	<0.0001	<0.0001	<0.0001
Siegel 2000 (urgency-frequency)	18-36 months	Baseline: 29	…	17.7 ±8.6	132.5 ±93.6	…	…	…	…
		With SNS: 29	…	10.6 ±6.6	225 ±162	…	…	…	…
		P value	…	<0.0001	<0.0001	…	…	…	…
Spinelli 2001	12 months	Baseline: 38	…	…	…	…	5.4±3.9	…	…
		With SNS: 17	…	…	…	…	1.1±1.6	…	…
		P value	…	…	…	…	0.001	…	…
Spinelli 2003	11 months	Baseline: 5	-	17.5 (2/5)	…	…	…	…	…
		With SNS: 5	80%	7.5 (2/5)	…	…	…	…	…
		P value	-	…	…	…	…	…	…
Spinelli 2005	6 months	Baseline: 20	…	10.05 ±3.12	…	…	4.86 ±3.05	…	3.71 ±3.00
		With SNS: 20	…	7.3 ±1.72	…	…	2.50 ±3.20	…	2.25 ±3.57
		P value	…	<0.001	…	…	<0.005	…	0.0069
Starkman 2007	7.2 months	Baseline: 22	-	…	…	…	…	…	4.2
		With SNS: 22	91% [a] (20/22)	…	…	…	…	…	1.1
		P value	-	…	…	…	…	…	<0.001
Sutherland 2007	22 months (3-162)	Baseline: 83	…	12.4±5.1	…	…	5.0±4.7	…	2.3±2.6
		With SNS: …	…	8.5±5.0	…	…	1.0±1.4	…	0.3±0.7
		P value	…	<0.0001	…	…	<0.0001	…	<0.0001

Table 45 continued Effectiveness outcomes: detrusor overactivity case series

Study	Follow-up	N= baseline & with SNS	Effectiveness outcomes - detrusor overactivity *continued...*						
			Response rate	Voids/day	Volume/ void (mL)	Maximum voided volume (mL)	Incontinent episodes/day	Severity of leakage	Pad use/day
Van Kerrebroeck 2007 (urge incontinence)	12 months	Baseline: 96	…	…	…	…	9.6 ±6.0	2.6 ±3.3 [b]	>5
		With SNS: 96	…	…	…	…	4.7 ±4.9	1.2 ±2.7	…
		P value	…	…	…	…	…	…	…
Van Kerrebroeck 2007 (urgency-frequency)	12 months	Baseline: 25	…	19.3 ±7.0	92.3 ±52.8	…	…	…	…
		With SNS: 25	…	13.0 ±7.9	169.9 ±118.2	…	…	…	…
		P value	…	…	…	…	…	…	…
Van Voskuilen 2007	15.5 months	Baseline: 21	-	11.7 ±8.9	160.2 ±70.7	…	9.5 ±8.7	…	…
		With SNS: 19	90% [a] (19/21)	7.3 ±3.4	231.1 ±119.5	…	3.3 ±2.2	…	…
		P value	-	0.1	0.001	…	0.17	…	…
Van Voskuilen 2006	64.2 months	Baseline: 107	-	…	…	…	…	…	…
		With SNS: 107	64% [g] (68/107)	…	…	…	…	…	…
		P value	-	…	…	…	…	…	…

NOTES:
[a] ≥50% improvement in presenting symptoms
[b] number of 'heavy' leaking episodes per day
[c] no daily leakage episodes after implantation
[d] severity of leakage ranked on a scale ranging from mild (1) to severe (3)
[e] severity of leakage ranked of a scale ranging from dry (0) to heavy (3)
[f] incontinence measured as grams of leakage
[g] based on patient response of 'good' or 'insufficient'

… = not reported
- = not applicable
NS = not statistically significant
Sig = statistically significant; exact p value not specified; exact p value not specified
Mean (range)
Mean ± standard deviation

Table 46 Durability of effectiveness outcomes: detrusor overactivity

Study	n= outcome timepoint	Durability of effectiveness outcomes – detrusor overactivity						
		Response rate	Voids/day	Volume/ void (mL)	Maximum voided volume (mL)	Incontinent episodes/day	Severity of leakage	Pad use/day
Bosch 2000	Baseline: 45	…	13.2 (10.2-15.5)	129 (101-179)	…	7.1 (4.9-9.2)	…	5.4 (3.9-8.6)
	6 months: 44	…	8.3 (7.1-10.7)	176 (132-233)	…	1.3 (0-3.8)	…	1.2 (0-3.2)
	P value	…	0.0001	0.0001	…	0.0001	…	0.0001
	12 months: 42	…	8.3 (6.6-9.3)	199 (146-233)	…	1.0 (0-3.7)	…	1.5 (0-3.0)
	P value	…	0.0001	0.0001	…	0.0001	…	0.0001
	24 months: 29	…	8.3 (7.4-10.0)	187 (108-210)	…	1.7 (0-4.3)	…	1.7 (0-4.0)
	P value	…	0.0001	0.009	…	0.0001	…	0.0001
	36 months: 24	…	9.0 (7.3-10.5)	173 (127-219)	…	0.5 (0-3.2)	…	1.5 (0-3.5)
	P value	…	0.0001	0.024	…	0.0001	…	0.0001
	48 months: 21	…	9.7 (7.9-10.7)	171 (112-204)	…	1.0 (0-3.3)	…	1.0 (0-3.1)
	P value	…	0.0002	0.044	…	0.0001	…	0.0001
	60 months: 19	…	9.0 (7.7-12.2)	150 (111-193)	…	0.7 (0-4.3)	…	1.3 (0-3.7)
	P value	…	0.0001	0.087	…	0.0001	…	0.0001
Cappellano 2001 (detrusor instability)	Baseline: 47	…	…	…	…	5.8±4.2	…	…
	3 months: …	…	…	…	…	0.6±1.0	…	…
	P value	…	…	…	…	…	…	…
	6 months: …	…	…	…	…	1.1±2.1	…	…
	P value	…	…	…	…	<0.01	…	…
	9 months: …	…	…	…	…	0.8±1.2	…	…
	P value	…	…	…	…	…	…	…
	12 months: …	…	…	…	…	0.9±1.5	…	…
	P value	…	…	…	…	<0.01	…	…
	18 months: …	…	…	…	…	1.2±1.5	…	…
	P value	…	…	…	…	…	…	…
Hedlund 2002	Baseline: 13	…	10.0±1.1	195±25	…	…	579±176[a]	8.3±1.3
	6 months: 12	…	8.6±0.6	256±30	…	…	93±60	2.1±0.7
	P value	…	NS	<0.05	…	…	<0.01	<0.01
	12 months: 9	…	8.0±0.6	255±27	…	…	16±8	1.3±0.4
	P value	…	NS	<0.05	…	…	<0.01	<0.01
	24 months: 7	…	7.0±0.7	289±37	…	…	9±1	0.6±0.4
	P value	…	NS	<0.05	…	…	<0.05	<0.05

Table 47 continued **Durability of effectiveness outcomes: detrusor overactivity**

Study	n= outcome timepoint	Durability of effectiveness outcomes – detrusor overactivity *continued...*						
		Response rate	Voids/day	Volume/ void (mL)	Maximum voided volume (mL)	Incontinent episodes/day	Severity of leakage	Pad use/day
Roupret 2004	Baseline: 6	-	…	…	…	…	…	…
	6 months: 6	50%[c] (3/6)	…	…	…	…	…	…
	P value	-	…	…	…	…	…	…
	12 months: 6	17% (1/6)	…	…	…	…	…	…
	P value	…	…	…	…	…	…	…
Spinelli 2001	Baseline: 37	14%[d] (5/37)	…	…	…	…	…	…
	3 months: 28	57% (16/28)	…	…	…	…	…	…
	P value	<0.001	…	…	…	…	…	…
	6 months: 26	65% (17/26)	…	…	…	…	…	…
	P value	<0.001	…	…	…	…	…	…
	9 months: 11	55% (6/11)	…	…	…	…	…	…
	P value	<0.003	…	…	…	…	…	…
	12 months: 17	59% (10/17)	…	…	…	…	…	…
	P value	<0.001	…	…	…	…	…	…
	18 months: 7	43% (3/7)	…	…	…	…	…	…
	P value	<0.04	…	…	…	…	…	…
Van Kerrebroeck 2007 (urge incontinence)	Baseline: 96	…	…	…	…	9.6±6.0	2.6±3.3	>5
	12 months: …	…	…	…	…	4.7±4.9	1.2±2.7	…
	P value	…	…	…	…	…	…	-
	60 months: 65	…	…	…	…	3.9±4.0	0.8±1.7	1.8
	P value	…	…	…	…	<0.001	<0.001	<0.001
Van Kerrebroeck 2007 (urgency-frequency)	Baseline: 25	…	19.3±7.0	92.3±52.8	…	…	…	…
	12 months: …	…	13.0±7.9	169.9±118.2	…	…	…	…
	P value	…	…	…	…	…	…	…
	60 months: 13	…	14.8±7.6	165.2±147.7	…	…	…	…
	P value	…	<0.001	<0.001	…	…	…	…

NOTES: [a] expressed as grams of leakage
[b] number of 'heavy' leaking episodes per day
[c] no leakage, urgency-frequency or pad use
[d] completely dry
… not reported
(range)
± standard deviation

Table 47 Effectiveness outcomes by implantation method: detrusor overactivity

	1-stage implantation							2-stage implantation			
	Bosch 2000 n=42	**Edlund 2000 n=9**	**Groenendijk 2007 n=15**	**Hedlund 2002 n=14**	**Latini 2006 n=29**	**Roupret 2004 n=6**	**Weil 2000 n=20**	**Latini 2006 n=12**	**Scheepens 2002 n=7**	**Spinelli 2003a n=5**	**Starkman 2007 n=22**
Response	…	…	80% [a] (12/15)	100%[b] (14/14)	…	17%[c] (1/6)	…	…	…	80% [d] (4/5)	91% [a] (20/22)
Voids/day	Decreased	…	…	Decreased	…	Decreased	…	…	Decreased	…	…
P-value	0.0001	…	…	NS	…	…	…	…	0.05	…	…
Volume/void	Increased	…	…	Increased	…	Increased	…	…	Increased	…	…
P-value	0.0001	…	…	<0.05	…	…	…	…	0.004	…	…
IE/day	Decreased	Decreased	Decreased	…	Decreased	Decreased	Decreased	Decreased	Decreased	…	…
P-value	0.0001	0.01	0.002	…	Significant	…	<0.0005	Significant	0.079	…	…
Pad use/day	Decreased	Decreased	Decreased	Decreased	…	…	Decreased	…	Decreased	…	Decreased
P-value	0.0001	0.07	0.004	<0.01	…	…	<0.0005	…	0.003	…	<0.001
Severity	…	Decreased	…	Decreased	…	…	…	…	Decreased	…	…
P-value	…	0.02	…	<0.01	…	…	…	…	0.041	…	…

NOTES: 'increased' or 'decreased' represents summary measure comparison pre- and post-implantation. IE incontinent episodes; …not reported

[a] ≥50% improvement

[b] total continence &/or >50% improvement

[c] no leakage, no urgency-frequency, no pad use

[d] continence restored & frequency normalised

Table 48 Patient-related quality of life outcomes: detrusor overactivity

Study	Outcome timepoint	n=	Patient-related quality of life outcomes – detrusor overactivity				
			Incontinence Impact Questionnaire (IIQ) score	QoL questionnaire score [a]	Subjective symptom improvement	% who would have the treatment again	% who would recommend the treatment to friend/relative
Aboseif 2002	24 months (mean)	43	…	…	>50%: 77% (33/43)	…	77% (33/43)
Amundsen 2002	7.8 months (mean)	Pre: 12	250 ±64	…	…	…	…
		Post: 12	62 ±45	…	…	…	…
		P value	0.03	…	…	…	…
Amundsen 2005	29 months (mean)	Pre: 55	…	…	…	…	…
		Post: 55	…	…	…	…	…
		P value	0.02	…	…	…	…
Cappellano 2001 (detrusor instability)	18 months	Pre SNS: 47	…	34.4 ±22.8	…	-	
		3 months: …	…	76.3 ±21.8	…	93%	96%
		P value	…	<0.001	…	-	-
		6 months: …	…	83.6 ±17.3	…	…	…
		P value	…	<0.001	…	…	…
		9 months: …	…	74.9 ±25.4	…	…	…
		P value	…	<0.01	…	…	…
		12 months: …	…	72.7 ±28.8	…	…	…
		P value	…	<0.01	…	…	…
		18 months: …	…	83.8 ±16.6	…	90%	100%
		P value	…	<0.01	…	-	-
Kessler 2007	24 months (median)	…	…	…	80% (44%-99%)	…	…
Spinelli 2001 (detrusor instability)	18 months	Pre SNS: 41		33.1			
		3 months: 41		74.7			
		P value		<0.001			
		6 months: 41		80.5			
		P value		<0.001			
		12 months: 41		69.6			
		P value		<0.001			
		18 months: 41		73.7			
		P value		…			

[a] Wagner T., Patrick D., Bavendam T. et al. 1996. Quality of life of persons with urinary incontinence: development of a new measure. Urology; 47:67. (0=worst; 100=best)

Table 49 Effectiveness outcomes: urinary retention case series

Study	Follow-up	n= baseline & with SNS	Effectiveness outcomes – urinary retention					
			Response rate	Voids/day	Volume/void (mL)	Post-void residual volume (mL)	Catheterisations/ day	Volume/ catheterisation (mL)
Aboseif 2002	24 months	Baseline: 20	-	…	44.3	325.3	…	…
		With SNS: 20	90%[a] (18/20)	…	195.2	59.2	…	…
		P value	-	…	<0.05	<0.05	…	…
Dasgupta 2004	37 months	Baseline: 26	-	…	…	…	…	…
		With SNS: 26	77%[a] (20/26)	…	385 (96-901)	75 (0-479)	1 (3 patients)	…
		P value	-	…	…	…	…	…
Datta 2008	48 months	Baseline: 60	-	…	…	…	…	…
		With SNS: 60	72%[a] (43/60)	…	…	100 (0-420)	CISC: 13 patients	…
		P value	-	…	…	…	…	…
De Ridder 2007	43.4 months	Baseline: 62	-	…	…	…	…	…
		With SNS: 62	55%[b] (34/62)	…	…	…	…	…
		P value	-	…	…	…	…	…
Elhilali 2005	…	Baseline: 9	-	…	…	…	…	…
		With SNS: 9	78% (7/9)	…	…	…	…	…
		P value	-	…	…	…	…	…
Groenendijk 2007	60 months	Baseline: 2	-	…	…	…	…	…
		With SNS: 2	50%[b] (1/2)	…	…	…	…	…
		P value	-	…	…	…	…	…
Kessler 2007	12 months (median)	Baseline: 13	-	3 (0-6)	…	…	4 (2-4)	…
		With SNS: 9	69% (9/13)	5 (5-6)	…	…	0 (0-0)	…
		P value	-	0.23	…	…	0.001	…
Scheepens 2002	60 months	Baseline: 7	…	…	152.5±212.6	…	4.1±2.3	302.7±128.5
		With SNS: 7	…	…	352.9±119.5	…	1.9±2.0	70.7±40.4
		P value	…	…	0.017	…	0.024	0.027
Siegel 2000	18-36 months	Baseline: 42	…	…	…	…	5.6±3.5	343±167
		With SNS: 42	…	…	…	…	…	91.4±154.6
		P value	…	…	…	…	…	<0.0001
Spinelli 2001	3 months	Baseline: 23	4% [c] (1/23)	…	…	<50mL: 8% (2/24)	…	…
		With SNS: 15	67% [c] (10/15)	…	…	<50mL: 67% (10/15)	…	…
		P value	<0.001	…	…	…	…	…
Spinelli 2003	11 months	Baseline: 7	-	…	…	334	3.1	…
		With SNS: 7	100%[a]	…	…	85	0.7	…
		P value	-	…	…	…	…	…

Table 49 continued **Effectiveness outcomes: urinary retention case series**

Study	Outcome timepoint	n= Baseline & With SNS SNS	Effectiveness outcomes – urinary retention *continued...*					
			Response rate	Voids/day	Volume/void (mL)	Post-void residual volume (mL)	Catheterisations/ day	Volume/ catheterisation (mL)
Spinelli 2005	6 months	Baseline: 21	…	3.17±3.49	…	…	3.96±1.22	328.39±83.32
		With SNS: 21	…	5.57±1.94	…	…	1.19±1.40	99.25±125.22
		P value	…	<0.001	…	…	<0.001	<0.001
Sutherland 2007	22 months	Baseline: 21	…	8.8±5.0	…	…	2.2±2.9	…
		With SNS: 21	…	8.6±4.2	…	…	1.7±3.0	…
		P value	…	NS	…	…	NS	…
Van Kerrebroeck 2007	60 months	Baseline: 31	…	…	…	…	5.3±2.8	379.9±183.8
		With SNS: 31	…	…	…	…	1.9±2.8	109.2±184.3
		P value	…	…	…	…	<0.001	<0.001
Van Voskuilen 2007	15.5 months	Baseline: 10	-	3.7 ±3.8	123.3 ±141.7	…	5.44 ±1.6	297.6 ±76.8
		With SNS: 9	90% [d] (9/10)	4.2 ±2.4	248.3 ±146.0	…	1.2 ±1.7	111.6 ±158.1
		P value	-	NS	NS	…	NS	NS
Van Voskuillen 2006	70.5 months	Baseline: 42	-	…	…	…	…	…
		With SNS: 42	76% [e] (32/42)	…	…	…	…	…
		P value	-	…	…	…	…	…

NOTES:
[a] number of patients able to spontaneously void
[b] number of patients able to void without requiring permanent or intermittent catheterisation
[c] zero catheterisations per day
[d] >50% improvement in at least one relevant voiding variables
[e] based on subjective patient response of 'good' or 'insufficient'
… not reported
CISC clean intermittent self-catheterisation

Table 50 Effectiveness outcomes: detrusor overactivity case series

Study	Mean outcome timepoint	n= pre & post SNS	Effectiveness outcomes				
			Response rate	Voids/day	Volume/void (mL)	Nocturia episodes	Pain
Comiter 2003	14 months	Pre: 17	-	16.9 ±4.6	111 ±45	4.5 ±2.7	5.8 ±2.2[b]
		Post: 17	94%[a] (16/17)	8.4 ±3.5	264 ±102	1.7 ±1.6	1.6 ±1.5
		P value	-	<0.01	<0.01	<0.01	<0.01
Elhilali 2005	6.45 years	Pre: 4	-	…	…	…	…
		Post: 4	25% (1/4)	…	…	…	…
		P value	-	…	…	…	…
Kessler 2997	10 months (median)	Pre: 7	…	…	…	…	8 (8-9) [b]
		Post: 7	…	…	…	…	2 (1-4)
		P value	…	…	…	…	0.03
Peters 2003	5.6 months	Pre: 26	…	24.7	…	5.7	…
		Post: 26	…	12.2	…	2.3	71% reported less pain
		P value	…	<0.001	…	<0.001	…
Peters 2004	15.4 months	Pre: 21	-	…	…	…	81.6 [d]
		Post: 21	95% [c] (20/21)	…	…	…	52.0
		P value	-	…	…	…	0.015
Steinberg 2007	14.1 months	Pre: 15	…	17.3±6.7	…	4.4±2.5	…
		Post: 15	…	6.8±2.8	…	1.73±1.7	…
		P value	…	<0.001	…	<0.001	…

[a] Improvement in all evaluation parameters from baseline to last post-operative visit
[b] scale of 1 – 10, 10 being greater pain
[c] patient self-reported moderate or marked improvement in pain
[d] mean narcotic dose (mg/day intramuscular morphine dose equivalent)

Appendix J Acronyms & abbreviations

AIHW	Australian Institute of Health and Welfare
BDI	Beck Depression Index
CI	confidence interval
CPP	chronic pelvic pain
IC	interstitial cystitis
ICER	incremental cost-effectiveness ratio
IDO	idiopathic detrusor overactivity
IPG	implantable pulse generator
IQR	inter quartile range
MSAC	Medical Services Advisory Committee
NHMRC	National Health and Medical Research Council
PBS	painful bladder syndrome
PET	positron emission tomography
PNE	peripheral nerve evaluation
PVR	post-void residual
QOL	quality of life
RCT	randomised controlled trial
S3	third sacral nerve
SMM	standard medical management
SNM	sacral neuromodulation
SNS	sacral nerve stimulation
TGA	Therapeutic Goods Administration
UF	urgency-frequency
UR	urinary retention
UUI	urge urinary incontinence

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