EVIDENCE APPRAISAL
REPORT

Technoleg Iechyd Cymru
Health Technology Wales

The clinical and cost effectiveness of sacral nerve stimulation to treat faecal incontinence that cannot be controlled with conservative management

EAR Number: 003 (June 2018)	**FIELD:** Incontinence
	TYPE: Treatment

Technoleg Iechyd Cymru
Health Technology Wales

Evidence Appraisal Report[1]

Review of systematic reviews and additional primary studies

The clinical and cost effectiveness of sacral nerve stimulation to treat faecal incontinence that cannot be controlled with conservative management

1. Health problem

Faecal incontinence (FI) is the involuntary loss of solid or liquid faeces. Damage to the anal sphincter mechanism or its nerve supply, age-related degeneration of the sphincter, spinal injury, or other neurological causes can all lead to chronic FI (Thaha, 2015). The condition is underreported due to its stigmatising nature, but it is thought to affect approximately 500,000 people in the UK (NICE, 2007). FI is more likely to affect women than men.

FI is at first treated by conservative management. This can include any/all of a range of nonsurgical, noninvasive interventions, such as:

- dietary modifications
- lifestyle modifications
- behavioural therapy
- anti-diarrhoeal medication
- absorbent padding or plugs
- suppositories or enema
- transanal irrigation (Thaha, 2015; Duelund-Jakobsen, 2016; J Cornish 2018, expert comment)

Where conservative management fails, a range of surgical techniques can be used. Such treatments are associated with significant costs and morbidity rates, and do not always provide adequate relief to the patient (J Cornish 2018, expert comment; Duelund-Jakobsen, 2016).

2. Health technology

Sacral nerve stimulation (SNS) involves direct, chronic, low-voltage electrical stimulation of the sacral nerve roots, which can be used to restore function of the bowel and/or bladder. The exact mechanism of action by which SNS restores continence is not understood, but effects on the sensory afferent nerves appears most probable (ICI, 2017; Thaha, 2015).

[1] Rapid systematic literature search of published evidence and websites to identify the best clinical and economic evidence. This is critically evaluated by researchers and the draft Evidence Appraisal Report is issued to experts for review and discussed by Health Technology Wales multidisciplinary advisory groups.

The procedure involves insertion of an electrode through a sacral foramen (usually S3), which then stimulates the nerve roots via a battery-powered pulse generator. All patients undergo a trial period to determine whether they will be responsive to SNS (usually a threshold of at least 50% reduction in FI episodes is used). This can be done via two types of testing, both of which are conducted over a two week period:

- Percutaneous nerve evaluation (PNE): this test involves a thin single-electrode temporary wire being inserted with or without x-ray guidance, either in the operating theatre or in a clinic room. A temporary neurostimulator is attached and worn externally. If the patient is responsive, the temporary wires are removed and replaced with permanent tined lead, and the SNS device is inserted just under the skin.
- Tined lead testing: a permanent tined lead is inserted in an operating room with x-ray guidance, and a neurostimulator is worn externally for two weeks. If the trial is successful then the tined lead remains in place, and the external neurostimulator is removed and replaced with the SNS device, which is inserted under the skin (Duelund-Jakobsen, 2016; Medtronic personal communication).

Two SNS devices are commercially available in the UK: the Medtronic Interstim system, which obtained CE marking in 2004, and the Axonics r-SNM system, which received CE marking in 2016.

2.1. Welsh context

In NHS England, SNS is offered to some adult patients with FI in line with a Clinical Commissioning Policy Statement (NHS England, 2013). This states that the treatment should only be offered to patients who meet all of a number of criteria, including disease that is severe and life-limiting, has not responded to conservative management, sphincter surgery is deemed inappropriate, and has improved after a trial simulation period. However, no equivalent policy exists in NHS Wales, and SNS is not available in NHS Wales.

In 2004, the National Institute of Health and Care Excellence (NICE) issued Interventional Procedures Guidance on the use of SNS (NICE, 2004). This guidance states that the evidence on the safety and efficacy of SNS for FI appears adequate to support the use of SNS. A NICE guideline on management of FI in adults was published in 2007. This states that SNS should be offered to people with FI in whom sphincter surgery is deemed inappropriate (either people with an intact anal sphincter, or those in whom sphincter surgery is contraindicated), and only after a successful trial stimulation period (NICE, 2007).

Some people in Wales have received SNS, either via approval of treatment on a case-by-case basis, or via privately funded treatment, but as SNS is not carried out at any Welsh centres, this necessitates travel to England for treatment.

As with other surgical techniques, SNS is intended as a treatment for people who have FI that cannot be managed by more conservative methods. In NHS Wales, commonly used surgical treatments in this scenario are the injection of bulking agents or creation of a stoma. People with FI due to sphincter defect may be offered sphincter repair or replacement initially; if this treatment fails, these people may also be candidates for SNS.

3. Evidence search methods

This assessment aims to evaluate the clinical and cost effectiveness of SNS compared to other treatment options for people whose FI cannot be managed by more conservative methods.

To identify clinical and cost effectiveness evidence for this assessment, HTW staff completed a literature search on 20 March 2018. Inclusion criteria were developed using the PICO framework in collaboration with the topic proposer and the HTW Assessment Group. The PICO framework is outlined in Appendix 1.

Findings of the literature search are summarised in Appendix 2. A systematic review published in 2015 (Thaha, 2015) was identified with similar inclusion criteria to this assessment. The findings of the systematic review by Thaha and colleagues (2015) are used as the basis for the clinical effectiveness evidence summarised in this report. In addition, the literature was searched for other relevant randomised controlled trials or randomised crossover trials published subsequent to the last search date of the review by Thaha and colleagues. The literature search was also screened for cost effectiveness evidence with no limits on publication date.

4. Clinical effectiveness

4.1. Systematic review (Thaha, 2015)

A Cochrane Review published in 2015 assessed the effectiveness of SNS for the treatment of faecal incontinence in adults. The review also studied the use of SNS to treat constipation, but this is outside the scope of this assessment. The inclusion and exclusion criteria of the Cochrane Review (listed in Appendix 3) were closely aligned with the selection criteria of this assessment (Appendix 2).

Six trials were identified that assessed the effectiveness of SNS for FI. These trials enrolled a total of 219 people. Individual trial characteristics are summarised in Table 1. Three of the studies (Leroi, 2005; Thin, 2015; Tjandra, 2008) recruited people with FI who had not responded to conservative management. The remaining studies either did not specifically recruit patients who had not responded to conservative treatment (Vaizey, 2000), or did not report patients' previous treatment (Kahlke, 2015; Sorenson, 2010).

All of the trials studied SNS based on the Medtronic Interstim system. Two trials compared a group of people who were treated with SNS to a group who received a control treatment (optimal medical therapy and percutaneous tibial nerve stimulation [PTNS] in the trials by Tjandra, 2008 and Thin, 2015 respectively). The remaining four trials used a blinded crossover design: after implantation, outcomes were assessed in patients when their stimulator was either turned on or off. The length of the 'on' and 'off' periods varied from one week to one month. This crossover design allowed both patients and investigators to remain blinded to whether the stimulator was 'on' or 'off'. By contrast, the nature of the control interventions in the randomised trials meant that patients were not blinded to the treatment they received.

4.2. Additional studies

One additional randomised trial was identified, which was published after the review by Thaha et al. This trial (Rydningen, 2017) compared people treated with SNS (n = 30) to a group treated with bulking agent injection (n = 26). The trial used SNS based on the Medtronic Interstim system, and recruited patients with FI that had not responded to optimal conservative management. Further study characteristics are outlined in Table 1.

4.3. Clinical effectiveness outcomes

SNS was compared to three different control treatments, and outcomes were compared for SNS-implanted patients during 'on' and 'off' periods as part of the crossover trials. The following section summarises

outcomes for SNS compared to each control treatment. Full results for all relevant reported outcomes are reported in Appendices 4 and 5.

SNS vs optimal medical therapy (Thaha, 2015; Tjandra, 2008)

Evidence from one randomised trial suggests that people treated with SNS experience fewer episodes of incontinence per week compared to people who receive optimal medical therapy (mean difference [MD] −6.30, 95% confidence intervals [CI] −10.34 to −2.26). People treated with SNS also had lower Cleveland incontinence scores[2] (MD −12.90, 95% CI −13.58 to −12.22) and required pads for fewer days per week (MD −1.00, 95% CI −2.13 to 0.13). Better quality of life scores (measured with the Fecal Incontinence Quality of Life index) were also reported by people treated with SNS compared to optimal medical treatment. All outcomes were measured after 12 months of follow-up.

SNS versus PTNS (Thaha, 2015; Thin, 2015)

Evidence from one randomised trial suggests that people treated with SNS experience fewer episodes of incontinence per week compared to people who receive PTNS (MD −3.20, 95% CI −7.14 to 0.74, measured after 6 months of follow-up). Cleveland incontinence scores were also lower for people treated with SNS (MD −3.00, 95% CI −6.74 to 0.74, measured after 6 months of follow-up). No significant differences in quality of life were reported between the treatments (measured using Fecal Incontinence Quality of Life index and EQ5D at 3 and 6 months follow-up).

SNS versus bulking agent (Rydningen, 2017)

Evidence from one randomised trial suggests that FI symptoms improve in people treated with SNS compared to bulking agent after 6 months follow-up (change in St Mark's score[3], MD −8.93, 95% CI −6.14 to −11.7). Twenty eight patients (93%) had a 50% or greater reduction in weekly FI episodes after SNS compared with nine patients (32%) treated with bulking agent ($p = 0.001$). Seventeen patients (57%) reported no weekly FI episodes 6 months after SNS compared with three patients (11%) treated with bulking agent ($p < 0.001$).

Crossover trials

Three crossover trials reported the number of episodes of FI experienced by patients during their 'on' and 'off' treatment periods. In three of the crossover trials (Leroi, 2005; Kahlke, 2015; Vaizey, 2000), patients reported fewer episodes of FI per week during the 'on' period than the 'off' treatment period, with the exception of a group of five patients in the trial by Leroi (2005) who stated a preference for the 'off' treatment period. In the same trial, 5 out of 19 patients who preferred the 'on' period had continence fully restored at the end of follow-up. In the trial by Sorenson (2010), there were no episodes of FI during either the 'on' or 'off' periods, but there were fewer episodes of soiling or passive leakage per week during the 'on' period than the 'off' period.

Two trials (Leroi, 2005; Kahlke, 2015) reported improved Cleveland incontinence scores during the 'on' compared to the 'off' treatment periods.

---

[2] The Cleveland Clinic Incontinence Score ranges from 0 (normal continence) to 20 (total incontinence).
[3] The St Mark's Incontinence Score ranges from 0 (normal continence) to 24 (total incontinence).

Table1. Summary of characteristics and design

Study reference	Methods, setting	Participants	Interventions	Outcomes	Summary of risks of bias
Studies included in Cochrane Review (Thaha, 2015)					
Kahlke, 2015	Randomised crossover trial 2009 to 2011. Follow-up: 3 months. Setting: single-centre, Germany. Intention-to-treat analysis: no.	Inclusion/exclusion criteria: not stated. Enrolled: 16. Median age (SD): 55.5 years (11.8). Sex: all female (16). Duration of symptoms: mean (SD): 51.9 months (42.7). Received permanent implant: 16. Lost to follow-up: 2.	All patients had SNS through a staged implantation procedure between 2009 and 2011. After 26.8 months (median) following implantation 16 out of the 31 participants agreed to be randomised into a crossover design to stimulation 'on' or 'off', each period lasted for 3 weeks. After 6 weeks (i.e. the two periods) participants while blinded selected the preferred period ('on' or 'off') which was continued for a further 3 months. There was no treatment-free interval.	Frequency of bowel movements; frequency of FI; Cleveland Clinic Incontinence Score.	Unclear whether treatment allocation was concealed. Patients (n = 2) who withdrew from the study are not accounted for in the results.
Leroi, 2005	Randomised crossover trial. Follow-up: 3 months. Setting: multicentre, France. Intention-to-treat analysis: no.	Inclusion criteria: FI to solid or liquid stool or incapacitating urgency; failed conservative treatment; demonstrable unilateral bulbo- (or clitorido-) cavernosus reflex; informed consent given. Exclusion criteria: extensive external anal sphincter defect (defect that was considered to be the main cause of FI). Enrolled: 27. Median age (range): 57 years (33 to 73).	Before permanent implantation, participants underwent temporary stimulation for 8 to 15 days. Following permanent implantation, stimulation was continuous with a pulse width of 210 microseconds, a frequency of 14 pulses per second, and a current amplitude adapted to the participant's perception of perineal and anal sphincter muscle contraction. The stimulator was left on during defaecation and urinary voiding.	Episodes of FI; faecal urgency; delay in postponing defaecation; bowel movements; severity of incontinence; QOL; anal manometry. Severity of incontinence was graded by the Cleveland Clinic Incontinence Scoring System. The score ranged from 0 (normal continence) to 20 (maximum incontinence).	Unclear whether treatment allocation was concealed. Three participants prematurely discontinued from the trial before completing the crossover period, and are not accounted for in the results. A further five patients who stated a preference for the 'off' period at the end of crossover are also

Study reference	Methods, setting	Participants	Interventions	Outcomes	Summary of risks of bias
		Sex: male (3); female (31). Duration of symptoms: < 1 year (12); 1 to 5 years (12); 5 to 10 years (4); > 10 years (6). Received permanent implant: 27. Lost to follow-up: 3.	After a 1- to 3-month optimisation 'on' phase, participants were randomised to either: (A) stimulation 'on' for 1 month (intervention), or (B) stimulation 'off' for 1 month (control). After 1 month groups A and B were then crossed over to the alternative. There was no treatment-free interval. At the end of the second month, the preferred period ('on' or 'off') was continued for a further 3 months: if neither was preferred, the stimulator was turned on.	QOL was assessed with the French version of the FIQL questionnaire. In the questionnaire, four separate QOL domains were explored: lifestyle; coping/behaviour; depression/self-perception; and embarrassment.	excluded from the results.
Sorenson, 2010	Randomised crossover trial. Blinding: participant and investigator. Follow-up: 2 weeks. Setting: single centre, Denmark.	Inclusion/exclusion criteria: not stated. Enrolled: 7. Age (range): 67 years (60 to 87). Gender: male (1); female (6). Duration of symptoms: not stated.	SNS. Participants had undergone permanent implantation 12 months before the trial began. Patients were randomised to either: (A) stimulator 'on' for one week (intervention), or (B) stimulator 'off' for one week (control). After one week the patients were crossed over to the alternative. No treatment-free period between the weeks	Defaecations per week; FI episodes per week; urge episodes per week; passive leakage per week; soiling per week; anal manometry.	Unclear whether randomisation used random sequence generation, or whether allocation of treatment was concealed. Unclear whether all planned outcomes were reported.

Study reference	Methods, setting	Participants	Interventions	Outcomes	Summary of risks of bias
	Intention-to-treat analysis: no.				
Thin, 2015	Randomised controlled trial. Blinding: Investigator. Follow-up: 6 months. Setting: two centres, London, UK. Intention-to-treat analysis: yes.	Inclusion criteria: Age > 18 years; met NICE (2007) criteria for symptom severity and failure of previous conservative therapy. Exclusion criteria: inability to provide informed consent; severe concomitant medical condition precluding randomization to operative treatment; neurological diseases, such as diabetic neuropathy, multiple sclerosis and progressing Parkinson's disease; other medical conditions precluding stimulation, such as bleeding disorders, certain cardiac pacemakers, peripheral vascular disease; congenital anorectal anomalies or absence of native rectum as a result of surgery; present evidence of external full-thickness rectal prolapse; previous rectal surgery (rectopexy/resection) < 12 months ago; stoma in situ; chronic bowel disease, such as inflammatory bowel disease, chronic uncontrolled diarrhoea; anatomical limitations that would prevent successful placement of electrodes; pregnancy or intention to become pregnant; previous experience of SNS or PTNS.	SNS (n = 23) vs PTNS (n = 17).	FI episodes/week (total, urge and passive); symptom severity scoring with Cleveland Clinic Incontinence Score; QOL measurements using EQ-5D, FIQL and SF-36.	Unclear whether patients were blinded to treatment received. More patients withdrew from the SNS group (n = 4) than the control group (n = 1).

Study reference	Methods, setting	Participants	Interventions	Outcomes	Summary of risks of bias
		Enrolled: 40. Mean age: 59 years. Sex: male (1); female (39). Duration of symptoms: not stated.			
Tjandra, 2008	Randomised controlled trial, parallel groups Blinding: no Follow-up: 12 months. Withdrawals: 7. Setting: single centre, Australia. Intention-to-treat analysis: no.	Inclusion criteria: involuntary passage of solid or liquid stool at least once per week; refractory to medical therapy and pelvic floor exercises; and aged 35 to 86 years. Exclusion criteria: rectal prolapse; inflammatory bowel disease; congenital anorectal malformation; neurologic disorders such as Parkinson's disease, multiple sclerosis; spinal cord injury; stoma in situ; pregnancy; external anal sphincter defect of more than 120° of the circumference; bleeding diathesis; and mental or physical disability precluding adherence to study protocol. Enrolled: 120. Mean age (SD): 63.9 years (±13.2) in SNS group; 63 years (±12.1) in the control group. Sex: male (9); female (111). Duration of symptoms: not reported. Received permanent implant: 53. Lost to follow-up: none.	SNS (n = 53). Peripheral nerve evaluation for at least 7 days; then permanent implantation in participants with ≥ 50% reduction in FI episodes per week or ≥ 50% reduction in number of days with FI per week based on the two-week bowel diary). Optimal medical therapy (n = 60), including bulking agents, pelvic floor exercises with a team of dedicated physiotherapists, and dietary management on fluid and fibre with a team of dieticians.	Anorectal physiology; severity of incontinence; two-week bowel diary (number of incontinent episodes per week, days with incontinence per week, days with staining per week and days with pads per week); QOL. Severity of incontinence was assessed by Cleveland incontinence score. The score ranged from 0 (normal continence) to 20 (maximum incontinence). QOL was the FIQL index and the standard short form-12 health survey quality of life questionnaire (SF-12).	Participants were not blinded to the treatment they received (blinding would have been impractical due to the nature of the control treatment). Assessment of outcomes was also unblinded.

Study reference	Methods, setting	Participants	Interventions	Outcomes	Summary of risks of bias
Vaizey, 2000	Randomised crossover trial. Blinding: participant and investigator. Follow-up: the study consisted of two 2-week intervals with subsensory stimulation either 'on' or 'off'. Setting: single centre, UK. Intention-to-treat analysis: no.	Inclusion criteria: passive FI; intact external sphincter; informed consent given. Enrolled: 2. Age: 65 and 61 years. Gender: female (2). Duration of symptoms: 2.5 years and 3 years.	Participants had received permanent SNS implants 9 months previously. To implant the unilateral electrode (Medtronic InterStim model 3080), the sacral nerve root (usually S3) that produces the maximal anal response was identified via percutaneous needle stimulation. An incision over the sacrum allows access to the sacral foramen. The permanent electrode was inserted directly and secured to the sacral periosteum after checking its correct placement by stimulation. A connecting lead (model 7495) was then tunnelled to the anterior abdominal wall to be connected to the stimulator. The Implantable Pulse Generator (model 3023) is programmable using telemetry. The voltage required for stimulation was between 0.5 and 2 volts at a frequency of 15 pulses per second and a pulse width of 210 μs. Participants were randomly assigned to either: (A) stimulator 'on' for two weeks with subsensory stimulation (intervention), or (B) stimulator 'off' for two weeks. After two	Episodes of FI for liquid or solid stool; anal manometry; psychological assessment; QOL. QOL was assessed with the SF-36 instrument, score 0 (poor) to 100 (excellent), reporting the domains of role-emotional, general health, mental health, bodily pain, physical functioning, role-physical, social function, and vitality.	Unclear whether randomisation used random sequence generation, or whether allocation of treatment was concealed. Not all mentioned outcomes were reported (no results for psychological assessment). Two patients withdrew consent before entering treatment; outcomes reported for all other patients.

Study reference	Methods, setting	Participants	Interventions	Outcomes	Summary of risks of bias
			weeks patients were switched to the alternative. There were no treatment-free period between the weeks.		
Additional studies identified from literature searches					
Rydningen, 2017	Randomised controlled trial, parallel groups. Blinding: investigator only. Follow-up: 6 months. Setting: two centres, Norway. Intention-to-treat analysis: no.	Inclusion criteria: FI defined as a St Mark's incontinence score greater than 8; weekly episodes of passive and/or urge FI despite optimal conservative management; third- or fourth-degree perineal tears during childbirth diagnosed clinically; successful 3-week trial of percutaneous nerve evaluation (defined as a 50% or greater reduction of FI episodes). Enrolled: 58. Median age (IQR): 61 (50 to 67) years. Sex: all female (58). Duration of FI not reported; median 39 years since obstetric injury (IQR 25.5 to 44).	Intervention: SNS. Tined lead connected to an internal pulse generator (Interstim II 3058, Medtronic) placed in a subcutaneous pocket under local anaesthesia. Control: Bulking agent. Cross-linked porcine dermal collagen (Permacol®) injected into the submucosa just above the dentate line in each of the four quadrants of the anal canal. In the absence of adverse events, the procedure was repeated after 3 months if there were still weekly episodes of FI.	Primary outcome: change in St Mark's FI score between baseline and 6 months. Secondary outcomes: change in disease-specific QOL (FIQL) and generic QOL (Euroqual, EQ-5DTM); self-reported outcome assessment (satisfied/not satisfied), change in weekly FI episodes (recorded from a bowel habit diary).	Participants were not blinded to the treatment they received (blinding would have been impractical due to the nature of the control treatment). Outcomes assessed solely by patient (QOL, self-reported assessment of FI) are therefore at higher risk of bias than investigator-reported outcomes (which were assessed without knowledge of allocated treatment). Two patients withdrew consent before entering treatment; outcomes reported for all other patients.

Study reference	Methods, setting	Participants	Interventions	Outcomes	Summary of risks of bias

EQ5D: EuroQual 5-dimension quality of life questionnaire; FI: faecal incontinence; FIQL: faecal incontinence quality of life index; IQR: interquartile range; PTNS: percutaneous tibial nerve stimulation; QOL: quality of life; SD: standard deviation; SF-36: short-form 36 quality of life questionnaire; SNS: sacral nerve stimulation.

4.4. Long term outcomes

The randomised controlled studies record outcomes for a maximum of 12 months after SNS implantation. Longer term outcomes are available from a prospective single-arm study (Altomare, 2015) that followed up patients treated with SNS for a minimum of 60 months. Consecutive patients from ten European centres were recruited between January 1998 and December 2006. Of those recruited (n = 237), 9 were lost to follow-up; results are available for the remaining 228 after a median 84 months of follow-up.

At last follow-up, 194 patients met the criteria for successful treatment (at least 50 per cent improvement in the number of FI episodes, or of one of the two scoring systems for FI at the last follow-up, compared with baseline), and 136 achieved full continence. Table 2 shows outcomes at baseline and last follow-up.

Table 2. Outcomes at baseline and after a median of 84 months follow up for FI patients treated with SNS (Altomare, 2015).

Outcome	Baseline (pre-SNS implant)	Last follow-up (median 84 months after SNS implant)
FI episodes per week, median (IQR)	7 (3.5 to 11)	0.25 (0 to 3)
Cleveland incontinence score, median (IQR)	16 (13 to 18)	7 (4 to 12)
St Mark's score, median (IQR)	19 (16 to 22)	6 (2 to 12)
FI: faecal incontinence; IQR: interquartile range; SNS: sacral nerve stimulation.		

4.5. Safety

Four out of six trials included in the systematic review (Thaha, 2015) reported adverse events: the remaining two trials did not report any information on adverse events. The more recent randomised controlled trial by Rydningen (2017) also reported adverse events.

Tjandra et al (2008) reported the following adverse events in patients treated with SNS:

- implantation site pain (6%)
- seroma (2%)
- excessive tingling in the vaginal region (9%)

In the control group, the only adverse event reported was constipation as a result of treatment with loperamide (6/60 patients).

Thin (2015) reported that adverse events in SNS-treated patients included:

- mild ipsilateral leg pain during temporary testing (n = 1)
- stimulator-site pain following insertion of neurostimulator (n = 2)

Adverse events reported in the control group (treated with PTNS) were:paraesthesia (n = 1)

- mild discomfort in the foot directly after sessions of stimulation (n = 1)

Rydningen (2017) reported that all adverse events experienced by SNS-treated patients were minor. Nine patients (35%) reported adverse events, compared to seven (25%) in the control group. Specific adverse events reported after SNS treatment included:

- pain related to the implanted pulse generator (n = 1)
- leg pain (n = 1)
- deterioration of urinary function, which resolved after resetting the implanted pulse generator (n = 5)
- deterioration of urinary incontinence (n = 2; 90% of recruited patients had pre-existing urinary incontinence in addition to FI)

In the crossover study by Kahlke et al (2015), adverse events reported after implantation included:

- haematoma formation (n = 3)
- misplacement of tined lead (n = 1)
- pain at stimulator site (n = 1)

In the crossover study by Leroi et al (2005), 4 out of 27 patients who received a permanent implant experienced adverse events that required removal of the stimulator (three cases of unresolved pain and one case of recurrent infection). These adverse events occurred before the beginning of the cross over period; the authors did not report whether any adverse events occurred during the crossover period or during follow up.

Altomare (2015) reported complications experienced by 228 SNS-treated patients after a median of 84 months follow up. Minor complications occurred in 79 patients, 64 of which were device related. Pain was the most common adverse event (n = 23), requiring device removal in 12 patients and replacement in a further 7 patients.

4.6. Ongoing trials

The literature search identified three ongoing trials of SNS to treat FI: one randomised controlled trial and two randomised crossover studies. Table 3 summarises details of these ongoing studies. In 2017, the SAFARI trial was halted due to the withdrawal of the magnetic sphincter augmentation device (FENIX) by the manufacturer. Participants recruited before this point will be followed up and the results reported, but patient numbers will be lower than planned (J Cornish 2018, expert comment; K Nugent 2018, expert comment).

Table 3. Ongoing trials of SNS to treat FI

Study name, reference	Setting and design	Eligibility criteria	Interventions	Outcomes	Expected completion
SAFARI (Jayne, 2014; Williams, 2016)	Randomised controlled trial. UK, multicentre.	Aged ≥ 18 years; FI for more than 6 months; incontinent episodes of ≥ 2 per week; suitable candidate for surgery; anal sphincter defect < 180° as documented on endoanal ultrasound scan.	Intervention: SNS. Comparison: magnetic sphincter augmentation (FENIX device). Planned recruitment: 175 patients per treatment.	Primary outcome: proportion of successful treatments, defined as device in use and ≥ 50 % improvement in the Cleveland Clinic Incontinence Score (CCIS) at 18 months post-randomisation. Secondary outcomes: complications; quality of life; cost effectiveness.	Trial stopped prematurely.
SUBSoNIC (McAlees, 2017)	Randomised crossover trial. UK, multicentre.	Adults (18 to 75 years) with FI (at least 8 FI episodes in a 4-week screening period), failing conservative treatment.	All patients receive SNS. Intervention: 16 week 'on' period. Control: 16-week 'off' period (stimulator turned off). Planned recruitment: 90 patients in total	Primary outcome: reduction in FI events. Secondary outcomes: urgency, urge and passive FI episodes; use of loperamide; social functioning; St Mark's incontinence score; quality of life; adverse events.	Trial end date: 30 November 2020.

Study name, reference	Setting and design	Eligibility criteria	Interventions	Outcomes	Expected completion
NCT03261622 (Jakobsen, 2017)	Randomised crossover trial. Three centres, Norway and Denmark.	Adults with idiopathic FI or incontinence following external sphincter tear ≤ 160 degrees; ≥ 1 FI episode after optimized conservative treatment.	All patients receive SNS. Intervention: 16 week 'on' period. Control: 16-week 'off' period (stimulator set to 0.05 V). Estimated enrolment: 75 participants.	Primary outcome: change in number of incontinence episodes. Secondary outcomes: Wexner incontinence score; St Mark's incontinence score; quality of life; anal physiology.	Estimated study completion date November 2020.
FI: faecal incontinence; SNS: sacral nerve stimulation.					

5. Cost effectiveness

Cost-effectiveness evidence identified from the literature search is summarised in Table 4. A range of health economic evaluations have been undertaken that assess the cost effectiveness of SNS and vary widely in methods, healthcare perspectives, clinical inputs and publication date. This results in a difficult appraisal of the cost effectiveness of SNS within the NHS. The general consensus within the literature is that SNS offers an increased quality of life for patients for a moderate increase in NHS costs.

Table 4. Health economic evaluations of SNS.

Reference	Year	Country	Approach	Clinical outcome	ICER
Pochopien, 2015	2015	UK	Cost utility analysis based on optimising the order of treatment	QALY	£14,357
Van Wunnik, 2012	2012	Netherlands	Cost effectiveness analysis based on a Markov model structure to evaluate SNS.	QALY	Dominates current surgical treatment
Leroi, 20111	2011	France	Cost effectiveness analysis of SNS for FI patients (2 year period)	> 50% continence severity score	€185,160
Brosa, 2008	2008	Spain	Cost effectiveness analysis based on a Markov model to evaluate SNS with Interstim	Symptom free years and QALYs	€16,181 to €22,195 per QALY
Dudding, 2008	2008	UK	Cost utility analysis using a decision tree (7 year) with SF-36 QOL	QALYs	£25,070 per QALY
Hetzer, 2006	2006	Switzerland	Cost analysis only	Success rates	No ICER reported; permanent stimulation cost estimated at €11,292
Centre for Evidence-based purchasing	2010	UK	Model based Cost utility analysis	QALYs	£22,784 per QALY (10 years) falls to £18,839 at 12 years

FI: faecal incontinence; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; QOL: quality of life; SNS: sacral nerve stimulation.
[1] This study is comparably short and does not report a QALY outcome.

The evaluation of the cost effectiveness of the use of SNS within the Welsh healthcare setting assessed the most recent, best quality UK-based evidence available. Unfortunately, the most recent UK evaluation

(Pochopien et al. 2015) is available only in abstract form at the time of this appraisal (as of June 2018). HTW will therefore focus on Dudding et al. (2008) as it offers the most detailed evaluation of the cost-effectiveness of SNS within the NHS treatment pathway.

5.1. Methods

Dudding et al. (2008) constructed a decision tree model utilising patient-level data collected through clinical records, questionnaires and bowel habit diaries from 70 patients (66 women and 4 men) with a median age of 55 years. All patients had SNS between 1996 and 2006 following an average of 7 years of FI and had failed to benefit from conservative treatments. The comparator is conservative treatment; this consists of regular constipating medications and attending one annual patient follow-up each year. Following a 2-week trial of SNS, a permanent neurostimulator and lead for those who reported a > 50% reduction in incontinence episodes was implanted. Only direct medical costs are considered in the model base case, but non-direct medical costs are incorporated in a scenario analysis of the extended impact.

Quality of life data was collected at baseline and then following latest treatment using the standard SF-36 questionnaire, whether this was temporary SNS or permanent implant. Quality of life outcomes were calculated over a 7 year period with each chance node and decision node having an attached total QALY estimate; these ranged from 4.25 to 4.89. Cost data was estimated based on treatment protocol and other costing resources. The costing method took into account 3 tiers of varied outcomes following the permanent SNS procedure. The tiered approach takes into account the likelihood of complications and the patient pathways that these would follow. The 3 tier costing structure allowed for the inclusion of a range of alternative outcomes (including adverse events) to be accounted for within the decision tree. The direct medical cost for a permanent SNS implantation was reported as £8,478 in 2005/2006.

5.2. Results

All of the 70 patients underwent temporary SNS with 61 reporting a > 50% reduction in FI episodes. While 10 of the 61 patients were still awaiting the procedure at the end of the study, data was available for 48 of the 51 patients with a permanent SNS implant. At the last follow-up, (median 24 months, ranging 1 to 106 months), 41 of the 48 patients had experienced improvements in their incontinence. Incontinence was reduced from a median of 6 events a week to a median of 0.5 events per week, with 19 patients reporting a complete cessation of the condition. Cost and QALYs estimated by the decision tree model are displayed in Table 5.

Table 5 Decision tree components

	Conservative treatment	SNS success[A] (87.14%)	SNS not successful[B] (12.86%)	SNS approach Total ([A+B])	Net difference
QALYs	4.25	4.55	4.41	4.54	0.29
Cost	£2,529	£9,812	£2,851	£9,795	£7,266

QALY: quality-adjusted life year; SNS: sacral nerve stimulation.
[A] 58.2% implant weighting. [B] 66.8% cost weighting for implant.

The resulting ICER was £25,070. The indirect cost approach results in a more favourable ICER as the costs associated with FI were diminished following treatment. However, no specific ICER was reported. The

sensitivity analysis used a one-way approach in varying the clinical effectiveness between the upper and lower bounds of the confidence interval and resulted in ICERs of £6,028 and £30,783, respectively.

5.3. Summary of findings

Dudding et al. (2008) reported an ICER above the £20,000 cost-effectiveness threshold. However, this information is dated. Updating this analysis with the most recent clinical and cost inputs was deemed problematic because the publication reporting was not detailed enough to replicate the methods. We adopted an indirect extrapolation of the current ICER for SNS, which required a modelling approach underpinned by several assumptions. Firstly, a linear relationship was assumed between the clinical outcomes and QALYs. This relationship allows the utilisation of metadata in updating the clinical effectiveness of SNS. The meta model averages the clinical outcomes within the literature; these are subsequently converted to QALYs according to the relationship offered by Dudding et al. (2008). The approach estimates a relationship between QALYs and clinical outcomes: a decrease in incontinence events results in an increase in QALYs. Two approaches are used to avoid issues resulting from heterogeneous scale. Table 6 outlines the numbers used to estimate the clinical-QALY ratio.

Table 6. The relationship between clinical outcomes and QALYs

	FI episodes	QALYs	Relationship
Comparator	6 median events	4.25	
SNS	0.5 median events	4.54	
Outcome (absolute)	−5.5	0.29	0.053 per reduced event
Outcome (ratio)	−91.6%		0.032 per 10% reduction
FI: faecal incontinence; QALY: quality-adjusted life year; SNS: sacral nerve stimulation.			

The meta-analysis utilises the clinical outcomes from Altomare et al. (2014) which is a large European multi-centre long-term outcomes review. Ten centres, including a UK centre, reported prospective data for a total of 407 patients who had temporary stimulation. A minimum of 5 years of follow-up data was required for inclusion in the review. A successful implantation was recorded for 58.2% of patients, lower than observed in Dudding et al. (2008). The clinical effectiveness was a reduction in FI from a median of 7 to 0.25 episodes per week. To scale the impact observed in Altomare et al. (2014) to that of the QALYs from Dudding et al. (2008) requires a weighting for effective implantation. A successful implantation would offer 0.41 QALYS according to the absolute change approach and 0.35 when using the ratio approach.

The economic costing update uses the current SNS device price to replace that used by Dudding et al. (2008) and then inflates the remaining cost difference to 2017 prices. The relative implantation percentage is taken into account. The SNS device is listed at £8,336. The outcomes are weighted according to the 58.2% implant success rate whilst the cost distribution follows the implant rate (taking into account those who had a lack of efficacy), which is 66.8%. In addition to the weighted costs built up from the successful and not successful arms there is an initial cost of £1,208 for the screening process, calculated from the Dudding et al. (2008) model. The resulting updated costs and outcomes, using the absolute approach (the reduction in event numbers), are presented in Table 7.

Table 7 Decision tree components using the absolute difference approach.

	Conservative treatment	SNS success[A]	SNS not successful[B]	SNS approach Total([A+B])	Net difference
QALYs	4.25	4.61	4.41	4.52A	0.27
Cost	£3,479	£10,970	£3,922	£9,838B	£6,359

[A] 58.2% implant weighting. [B] 66.8% cost weighting for implant.
QALY: quality-adjusted life year; SNS: sacral nerve stimulation.

The resulting ICER for the absolute group is £23,207, whilst the ratio group has an estimated ICER of £26,016. The lower ICER estimate for the absolute group reflects the higher QALY gains available when calculating benefits on a per event reduced method.

5.4. Additional modelling

Replacement of the battery can continue the benefits to the patient over a longer period. Extending the QALY benefits over 14 years to include a battery change reduces the ICER to £20,051. The battery change includes cost of the device and a day case visit. The device ICER decreases as the battery life increases over the base-case of 7 years.

To receive continence support items from the NHS, the patient's condition must meet the eligibility criteria set out by their clinical commissioning group, and the patients is required to have an assessment. An estimated eligibility and uptake rate of 20% of the patient group to receive 9 pads daily at a cost of (48p) each (£1,576 per year) was included into the base case model. The additional costs applied to both the conservative treatment group and the SNS not successful group. The resulting SNS net cost difference is £5,026, with an ICER of £18,344.

To test the impact of developments to the implantation process the rate of complications experienced in the Dudding et al. (2008) paper was reduced from 20.83% to 10.83%; this resulted an ICER of £22,914 when using the absolute approach.

5.5. Strengths of the literature and analysis

The Dudding et al. (2008) paper uses a detailed decision tree structure to account for the plausible outcomes following the screening for SNS. The assumptions are reasonable and the approach well implemented. The Altomare et al. (2015) paper benefits from a very large cohorts of patients offering long term clinical outcomes for SNS. The adapted analysis undertaken for this appraisal utilises the best available data to update a solid utility based decision tree to represent a 2017 view of the cost-effectiveness of SNS.

5.6. Limitations of the literature and analysis

- The Dudding et al. (2008) paper uses a small cohort with a short term clinical outcome and quality of life collection.
- The mapping of QALYs is unclear.
- The non-successful decision tree node offers the best ICER.
- There is uncertainty surrounding exact replication of the costing framework.

- Altomare et al. (2015) uses a varied comparator whilst offering a grouped clinical outcome.
- The updated analysis relies on a range of assumptions.
- The linear relationship between clinical outcomes and QALYs is plausible but cannot be verified.
- The updating of costs is based on a top-down consumer price index inflator method as opposed to a more accurate bottom-up approach (aside from the inclusion of the SNS device costs). This approach may add bias if there were significant alterations to the patient pathway over time.
- The clinical outcomes mapped from Altomare et al. (2015) are specific to those who have a successful experience with SNS. This is partially mitigated by accounting for complications in the structural model but this issue should still be noted. This is likely to overestimate the clinical inputs in comparison to Dudding et al. (2008) as the sub-group is comprised of only those deemed to be a clinical success.
- While there is evidence that benefits are sustained long-term, the model horizon is limited to 7 years. A longer time horizon would reduce the ICER.
- Alternative treatments that were made available following the publication of Dudding et al (2008) are not included into the modelling approach.

6. Organisational issues

No specific organisational issues were identified from the evidence searched. Expert feedback highlighted the existence of the National Audit of Continence Care, which assessed continence services (both FI and urinary incontinence) across England and Wales. The most recent report (Royal College of Physicians, 2012) highlighted that many continence services (FI or UI) are poorly integrated across acute, medical, surgical, primary, care home and community settings. This results in disjointed care for patients and carers. Gaps in organisational standards for continence care were identified, leading to gaps in clinical care. Where a person is found to have incontinence, diagnosis of causes and therefore curative treatment is often not provided. Overall adherence to the national guidance (NICE) for urinary and FI was found to be variable (Royal College of Physicians, 2012).

Clinicians require training on the implantation of SNS devices. Medtronic provide training and education courses via European Continuing Medical Training, as well as nurse training and training for follow-up such as device programming. Insertion of wires for the temporary stimulation period has in the past been performed under general anaesthetic, but the procedure can be performed in the outpatient setting under local anaesthetic.

The permanent stimulator is battery-operated; batteries last for several years but this may vary according to factors such as stimulation parameters. For the Medtronic Interstim II device, the manufacturer estimates the battery life to be 4 to 7 years; experts report that from clinical experience, batteries last between 5 and 10 years. Once the battery is depleted, replacement is required: the device incorporates a battery indicator to allow judgement on when replacement is needed. In the study by Altomare et al (2015), which followed up 228 patients for a median of 84 months, 17 patients required device removal and repositioning for dislocation or battery depletion. Rechargeable SNS systems are being developed and are anticipated to offer battery life of up to 15 years. The rechargeable Axonics r-SNM system is CE marked but is not yet available in the UK; launch is anticipated for late 2018. A rechargeable system is also being developed by Medtronic, but timescales for availability of this are not known.

7. Patient issues

The randomised trial by Thin et al. (2015), which compared SNS implantation to PTNS, collected qualitative data from a sample of ten patients who were interviewed before and after treatment: results were reported collectively and not by individual treatment.

The interviews found that that both treatments had similar, very high, acceptability levels. The authors identified nine positive themes emerging from the transcripts: improved ability to defer defaecation, improved self-confidence, improved hygiene, hope and optimism for the future, gaining control and freedom, returning to normality, reduced anxiety, feelings of support, and regret for postponing treatment initiation. Negative themes related to delays in treatment, absence from work and individual costs, distances travelled and time required to undergo therapy.

8. Conclusions

There is evidence from randomised trials about the clinical effectiveness of SNS compared to no treatment, bulking agent injection, or PTNS. No head-to-head trials were identified that compared SNS to stoma or any other surgical interventions. The evidence had some limitations: sample sizes in the studies were generally small (range 2–120 participants), and not all trials blinded patients and/or investigators to the treatment received. The majority of studies (Leroi, 2005; Thin, 2015; Tjandra, 2008; Rydningen, 2017) specifically recruited patients who matched the target population of this assessment: people with FI who had not responded to conservative management. The remaining studies either did not specifically recruit patients who had not responded to conservative treatment (Vaizey, 2000), or did not report patients' previous treatment (Kahlke, 2015; Sorenson, 2010). None of the trials accounted for patients for whom a trial SNS period was unsuccessful: the four crossover trials and one randomised trial included patients who had undergone permanent SNS implant, whilst the two randomised trials recruited any patients eligible for SNS, but only reported outcomes for those who progressed to permanent implant.

The evidence consistently shows that SNS reduces the frequency of FI episodes, and that SNS reduces the frequency of FI by a greater margin than PTNS, bulking agent injection, or optimal medical therapy. Quality of life and clinical incontinence scores (Cleveland or St Mark's incontinence scores) also improved after SNS treatment, but these did not all improve by a greater margin than the active treatments. It is not clear whether there are any established thresholds for clinical significance for these scoring systems (Y Maeda 2018, expert comment).

Comparative clinical evidence is available for a relatively short follow-up period (minimum 4 weeks; maximum 12 months). However, evidence from a multicentre European study that followed patients up for a median of 84 months after SNS implantation suggests that SNS is an effective long-term treatment: of 237 recruited patients, 194 (81.8%) had at least 50% reduction in FI frequency at last follow up, and 136 (57.3%) achieved full continence.

The published cost-effectiveness results suggest that SNS offers a sustained positive clinical outcome and improvement to QALYs at an increase in costs, which results in an ICER which is inconclusive. The updated analysis uses a structure offered by the literature and finds similarly scaled ICERs. Extending the model time horizon to a plausible longer term would improve the ICER and could be argued to be a more accurate estimate. Patients who experienced large improvements to their QALYs would theoretically result in lower ICERs even following device replacement.

9. Contributors

The HTW staff and contract researchers involved in writing this report were:

- D Jarrom – main author and systematic literature reviewer
- L Elston – second reviewer and quality assurance
- B Coles - literature search
- T Winfield and B Sewell - economic appraisal

The HTW Assessment Group advised on methodology throughout the scoping and development of the report.

The following experts provided comments on a draft of this report:

- J Cornish, Consultant Colorectal Surgeon, Cardiff and Vale University Health Board
- K Nugent, Consultant Colorectal Surgeon, University Hospital Southampton NHS Foundation Trust (responding on behalf of the Pelvic Floor Society)
- L Elstub, Managing Editor, Cochrane Incontinence Group
- N Hallas, Health Economics and Commissioning Manager, Medtronic
- Y Maeda, Senior Fellow, Sir Alan Parks Physiology Unit, St Mark's Hospital, Harrow

Their views were documented and actioned as appropriate. The views expressed in the final publication are those of HTW.

Review period

Two years after the date of publication, a high-level literature search will be undertaken to determine if there is new evidence that could alter the conclusions of this report. If so, the appraisal will be updated.

10. References

Altomare DF, Giuratrabocchetta S, Knowles CH, et al. (2015). Long-term outcomes of sacral nerve stimulation for faecal incontinence. British Journal of Surgery 102(4): 407-15.

Bank of England CPI inflation calculator. (2018). Available at: www.bankofengland.co.uk/monetary-policy/inflation

Brosa M, Muñoz-Duyos A, Navarro-Luna A, et al. (2008). Cost–effectiveness analysis of sacral neuromodulation (SNM) with Interstim for fecal incontinence patients in Spain. Current Medical Research and Opinion 24(3):907-18.

Dudding TC, Meng Lee E, Faiz O, et al. (2008). Economic evaluation of sacral nerve stimulation for faecal incontinence. British Journal of Surgery. 95(9): 1155-63.

Duelund-Jakobsen J, Worsoe J, Lundby L, et al. (2016). Management of patients with faecal incontinence. Therapeutic Advances in Gastroenterology 9(1): 86-97.

Hetzer FH, Bieler A, Hahnloser D, et al. (2006). Outcome and cost analysis of sacral nerve stimulation for faecal incontinence. British Journal of Surgery. 93(11):1411-7.

ICI: International Consultation on Incontinence (2017). 6th Edition. Ed: Abrams, Cardozo, Wagg, Wein (6th International Consultation on Incontinence, Tokyo, September 2016). Chapter 17: Surgery for Faecal Incontinence.

Jakobsen J. (2017). NCT03261622. Sacral Nerve Stimulation for Faecal Incontinence - Placebo or Clinical Effective. Available at: https://clinicaltrials.gov/show/NCT03261622

Jayne D, Croft J. (2014). Sacral nerve stimulation versus the FENIX magnetic sphincter augmentation for adult faecal incontinence: a randomised investigation (SaFaRI). Available at: http://www.isrctn.com/ISRCTN16077538

Kahlke V, Topic H, Peleikis HG, et al. (2015). Sacral nerve modulation for fecal incontinence: results of a prospective single-center randomized crossover study. Diseases of the Colon & Rectum. 58(2): 235-240.

Leroi AM, Parc Y, Lehur PA, et al. (2005). Efficacy of sacral nerve stimulation for fecal incontinence: results of a multicenter double-blind crossover study. Annals of Surgery. 242(5): 662-9.

Leroi AM, Lenne X, Dervaux B, et al. (2011). Outcome and cost analysis of sacral nerve modulation for treating urinary and/or fecal incontinence. Annals of Surgery. 253(4):720-32.

McAlees E, Tubby K. (2017). SUBSONIC: Subsensory sacral neuromodulation for incontinence. Available at: http://isrctn.com/ISRCTN98760715

NICE. (2013). Guide to the methods of technology appraisal. Process and methods PMG9. National Institute for Health and Care Excellence. Available at: www.nice.org.uk/process/pmg9/chapter/the-reference-case

NICE. (2004). Sacral nerve stimulation for faecal incontinence: Interventional procedures guidance IPG99. National Institute for Health and Care Excellence. Available at: www.nice.org.uk/guidance/ipg99

NICE. (2007). Faecal incontinence in adults: management. Clinical guideline CG49. National Institute for Health and Care Excellence. Available at: www.nice.org.uk/guidance/cg49

NHS England. (2013). Sacral nerve stimulation (SNS) for faecal incontinence (Adult). Clinical Commissioning Policy NHSE/A08/P/b. Available at: www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2013/08/a08-p-b.pdf

Pochopien M, Plisko R, Drzal R, et al. (2015). Cost-utility analysis of sacral nerve stimulation for the treatment of fecal incontinence refractory to conservative treatment: looking for optimal treatment path. Value in Health. 18(7): A359.

Royal College of Physicians (2012). National audit of continence care (NACC): pilot audit evaluation report. Available at: www.rcplondon.ac.uk/projects/outputs/national-audit-continence-care-nacc

Rydningen M, Dehli T, Wilsgaard T, et al. (2017). Sacral neuromodulation compared with injection of bulking agents for faecal incontinence following obstetric anal sphincter injury - a randomised controlled trial. Colorectal Disease. 19(5): O134-44.

Sorensen M, Thomsen F. (2010). Sacral nerve stimulation increases rectal sensitivity in patients with faecal incontinence: results of a randomised double-blinded crossover study (Abstract number 437). Proceedings of the joint meeting of the International Continence Society (ICS) and the International Urogynecological Association (IUGA). Toronto, Canada. 2010 Aug 23-27 International Urogynecology Journal 22(Suppl 2):S464-5.

Thaha MA, Abukar AA, Thin NN, et al. (2015). Sacral nerve stimulation for faecal incontinence and constipation in adults. Cochrane Database of Systematic Reviews 2015 (8) (CD004464).

Thin NN, Taylor SJ, Bremner SA, et al. (2015). Randomized clinical trial of sacral versus percutaneous tibial nerve stimulation in patients with faecal incontinence. British Journal of Surgery. 102(4): 349-58.

Tjandra JJ, Chan MK, Yeh CH, et al. (2008). Sacral nerve stimulation is more effective than optimal medical therapy for severe fecal incontinence: a randomized, controlled study. Diseases of the Colon & Rectum. 51(5): 494-502.

Van Wunnik BP, Visschers RG, van Asselt AD,et al. (2012). Cost-effectiveness analysis of sacral neuromodulation for faecal incontinence in The Netherlands. Colorectal Disease. 14(12): e807-14.

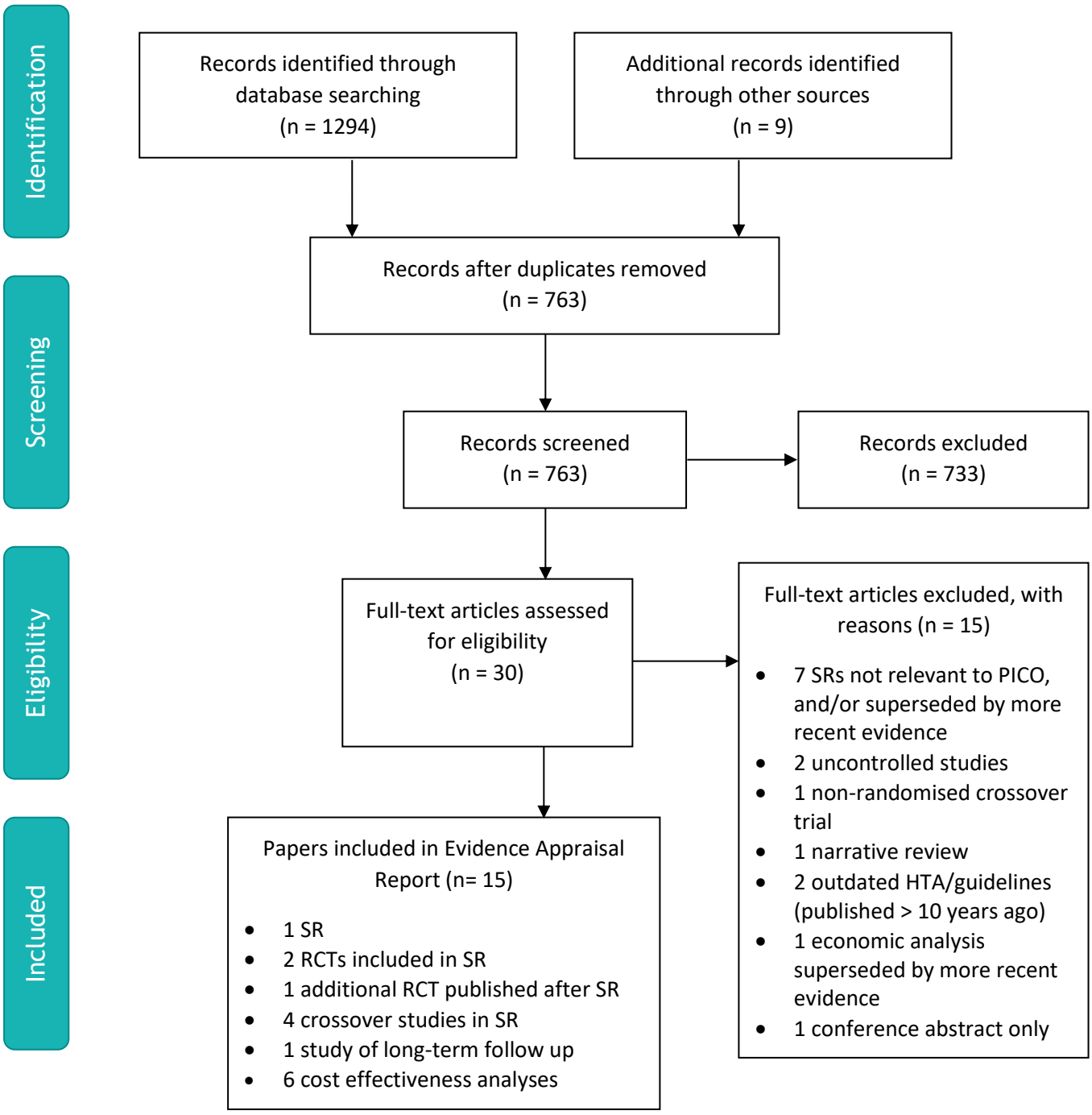
Vaizey CJ, Kamm MA, Roy AJ, et al. (2000). Double-blind crossover study of sacral nerve stimulation for fecal incontinence. Diseases of the Colon & Rectum. 43(3): 298-302.

Williams AE, Croft J, Napp V, et al.(2016). SaFaRI: sacral nerve stimulation versus the FENIX™ magnetic sphincter augmentation for adult faecal incontinence: a randomised investigation. International Journal of Colorectal Disease. 31(2): 465-72.

Appendix 1. Study selection criteria

P (population)	People with faecal incontinence that cannot be controlled with conservative management
I (intervention)	Sacral nerve stimulation
C (comparator(s))	No treatment Usual care (use of nappies, plugs etc.) Stoma Other surgical interventions (bulking agents; sphincter repair; artificial bowel sphincter; dynamic graciloplasty)
O (outcomes)	Cure or improvement of faecal incontinence, measured as any of: • number of patients with symptom improvement • change in number of episodes of incontinence • change in ability to defer defecation • change in frequency of use of pads/plugs • incontinence score Quality of life Adverse events/surgical complications

Appendix 2 - PRISMA flow diagram outlining selection of papers for clinical and cost effectiveness



Appendix 3. Criteria for considering studies in the Cochrane Review conducted by Thaha et al. (2015)

Inclusion criteria:

Types of studies: randomised, quasi-randomised and crossover trials.

Types of participants: adults with faecal incontinence or constipation[4], including functional, structural and neurological causes.

Types of interventions: one arm of the trial had to use a surgically implanted device to provide sacral nerve stimulation. Newer treatment modalities including magnetic and transcutaneous stimulation were also considered.

Comparators: mock, sham or placebo treatment; or any alternative active intervention considered appropriate by the trialists, such as dynamic graciloplasty, artificial bowel sphincter implants, stoma formation, absorbent pads, anal plugs, and physical or behavioural therapies.

Primary outcomes: (1) Faecal incontinence (number cured or improved, episodes of faecal incontinence, urgency, ability to defer defaecation, use of pads, use of anal plugs, incontinence score, and need for further treatment such as medication or surgery). (2) Quality of life (generic and condition-specific).

Secondary outcomes: (1) Surrogate measures, such as anorectal manometry (resting pressure, maximum squeeze pressure, rectal sensory threshold to balloon distention, sensation of urgency to balloon distention, and maximum tolerated rectal volume to balloon distention). (2) Adverse effects (infection or pain or both at the implantation site; displacement of the electrodes; technical failure requiring removal or change in urinary function, or both). (3) Health economics (costs, resource implications and cost-effectiveness or cost utility evaluation). (4) Other outcomes (other outcome measures quoted by trial authors and judged to be important by the authors of this review).

Exclusion criteria:

Trials in which both arms used active implanted sacral nerve stimulation.

[4] Constipation is not a subject of this assessment. Only outcomes for treatment of faecal incontinence are reported in this assessment.

Appendix 4. All clinical outcomes: randomised trials

Table 1: SNS vs optimal medical therapy (Tjandra 2008)

Outcome	SNS (n = 53)	Control (n = 60)	Treatment effect, mean difference (95% CI)
Episodes of faecal incontinence per week at 3 months follow up, mean (SD)	2.9 (6.3)	8.1 (14.1)	−5.20 (−9.15 to −1.25)
Episodes of faecal incontinence per week at 12 months follow up, mean (SD)	3.1 (10.1)	9.4 (11.8)	−6.30 (−10.34 to −2.26)
Days using pads per week, 3 months follow up, mean (SD)	1.6 (2.6)	3 (3.8)	−1.40 (−2.59 to −0.21)
Days using pads per week, 12 months follow up, mean (SD)	2.2 (3)	3.2 (3.1)	−1.00 (−2.13 to 0.13)
Days with incontinence per week, 3 months follow up, mean (SD)	1 (1.7)	2.9 (2.4)	−1.90 (−2.66 to −1.14)
Days with incontinence per week, 12 months follow up, mean (SD)	1 (1.7)	3.1 (3.1)	−2.10 (−3.01 to −1.19)
Cleveland Clinic Incontinence Score, 3 months follow up, mean (SD)	1.1 (1)	12.1 (2.1)	−11.00 (−11.60 to −10.40)
Cleveland Clinic Incontinence Score, 12 months follow up, mean (SD)	1.2 (1.8)	14.1 (1.9)	−12.90 (−13.58 to −12.22)
SF-12 Physical, 3 months follow up, mean (SD)	43.18 (11.68)	41.5 (9.89)	1.68 (−2.34 to 5.70)
SF-12 Physical, 12 months follow up, mean (SD)	42.22 (9.25)	40.5 (10.2)	1.72 (−1.87 to 5.31)
SF-12 Mental, 3 months follow up, mean (SD)	50.16 (10.41)	47.82 (10.66)	2.34 (−1.55 to 6.23)
SF-12 Mental, 12 months follow up, mean (SD)	49.22 (10.88)	48.22 (10.12)	1.00 (−2.89 to 4.89)
FIQL Lifestyle, 3 months follow up, mean (SD)	3.34 (0.72)	2.12 (0.91)	1.22 (0.92 to 1.52)
FIQL Lifestyle, 12 months follow up, mean (SD)	3.31 (0.72)	2.31 (0.89)	1.00 (0.70 to 1.30)
FIQL Coping/behaviour, 3 months follow up, mean (SD)	2.87 (0.8)	1.85 (0.92)	1.02 (0.70 to 1.34)
FIQL Coping/behaviour, 12 months follow up, mean (SD)	2.68 (0.87)	1.86 (0.88)	0.82 (0.50 to 1.14)
FIQL Depression/self-perception, 3 months follow up, mean (SD)	3.31 (0.77)	2.68 (0.65)	0.63 (0.37 to 0.89)
FIQL Depression/self-perception, 12 months follow up, mean (SD)	3.25 (0.8)	2.64 (0.84)	0.61 (0.31 to 0.91)
FIQL Embarrassment, 3 months follow up, mean (SD)	2.89 (0.85)	1.7 (0.67)	1.19 (0.91 to 1.47)
FIQL Embarrassment, 12 months follow up, mean (SD)	2.76 (0.94)	1.78 (0.61)	0.98 (0.68 to 1.28)

FIQL faecal incontinence quality of life index; SD: standard deviation; SNS: sacral nerve stimulation.

Table 2: SNS vs PTNS (Thin 2015)

Outcome	SNS (n = 15)	Control (n = 17)	Treatment effect, mean difference (95% CI)
Episodes of faecal incontinence per week at 3 months follow up, mean (SD)	2.8 (2.5)	5.8 (6.9)	−3.00 (−6.61 to 0.61)
Episodes of faecal incontinence per week at 6 months follow up, mean (SD)	3.1 (4.0)	6.3 (6.9)	−3.20 (−7.14 to 0.74)
Cleveland Clinic Incontinence Score, 3 months follow up, mean (SD)	10 (5.3)	11.7 (4.4)	−1.70 (−5.14 to 1.74)
Cleveland Clinic Incontinence Score, 6 months follow up, mean (SD)	9.1 (5.4)	12.1 (5.2)	−3.00 (−6.74 to 0.74)
EQ5D, 3 months follow up, mean (SD)	0.66 (0.28)	0.6 (0.38)	0.06 (−0.17 to 0.29)
EQ5D, 6 months follow up, mean (SD)	0.76 (0.22)	0.63 (0.37)	0.13 (−0.08 to 0.34)
FIQL Lifestyle, 3 months follow up, mean (SD)	−3.1 (0.8)	−2.9 (1)	−0.20 (−0.82 to 0.42)
FIQL Lifestyle, 6 months follow up, mean (SD)	−3 (0.9)	−2.8 (0.9)	−0.20 (−0.82 to 0.42)
FIQL Coping, 3 months follow up, mean (SD)	−2.5 (0.7)	−2.3 (0.8)	−0.20 (−0.72 to 0.32)
FIQL Coping, 6 months follow up, mean (SD)	−2.5 (0.8)	−2 (0.9)	−0.50 (−1.09 to 0.09)
FIQL Depression, 3 months follow up, mean (SD)	−2.7 (0.8)	−2.8 (0.8)	0.10 (−0.46 to 0.66)
FIQL Depression, 6 months follow up, mean (SD)	−2.7 (0.7)	−2.6 (0.9)	−0.10 (−0.66 to 0.46)
FIQL Embarrassment, 3 months follow up, mean (SD)	−2.5 (0.7)	−2.2 (0.8)	−0.30 (−0.82 to 0.22)
FIQL Embarrassment, 6 months follow up, mean (SD)	−2.6 (0.8)	−2 (0.8)	−0.60 (−1.16 to −0.04)

EQ5D: EuroQual 5−dimension quality of life questionnaire; FIQL faecal incontinence quality of life index; SD: standard deviation; SNS: sacral nerve stimulation.

Table 3: SNS vs bulking agent (Rydningen 2017)

Outcome	SNS (n = 30)	Control (n = 26)	Treatment effect, mean difference (95% CI)
Change in St Mark's Score, 6 months follow up, mean (SD)	−11.2 (5.3)	−2.3 (5.0)	−8.9 (−11.7 to −6.1)
Change in EQ5D, 6 months follow up, mean (SD)	0.059 (0.20)	0.028 (0.19)	0.031 (−0.073 to 0.14)
Change in FIQL Lifestyle, 6 months follow up, mean (SD)	1.05 (0.84)	0.15 (0.61)	0.90 (0.50 to 1.30)
Change in FIQL Coping, 6 months follow up, mean (SD)	1.25 (0.84)	0.20 (0.72)	1.05 (0.62 to 1.47)
Change in FIQL Depression, 6 months follow up, mean (SD)	0.65 (0.66)	0.14 (0.64)	0.52 (0.16 to 0.87)
Change in FIQL Embarrassment, 6 months follow up, mean (SD)	1.28 (0.84)	0.36 (0.77)	0.95 (0.50 to 01.40)

EQ5D: EuroQual 5-dimension quality of life questionnaire; FIQL faecal incontinence quality of life index; SD: standard deviation; SNS: sacral nerve stimulation.

Appendix 5. All clinical outcomes: crossover trials

Table 1. Outcomes from Kahlke 2015

OUTCOME	BASELINE	ON PERIOD (3 weeks)	OFF PERIOD (3 weeks)	FOLLOW UP PERIOD (3 months)
FI episodes per week, mean (SD)	18 (19.6)	1 (1.7)	8.4 (8.7)	0.3 (0.5)
CCIS, mean (SD)	16 (4.6)	8.7 (3.6)	14.6 (4.6)	6.4 (3.3)
CCIS: Cleveland Clinic Incontinence Score; FI: faecal incontinence; SD: standard deviation.				

Table 2. Outcomes from Leroi 2015

OUTCOME	BASELINE	ON PERIOD (1 month)	OFF PERIOD (1 month)	FOLLOW UP PERIOD (3 months)
FI episodes per week, median (range)	3.5 (0 to16)	0.7 (0 to 5)	1.7 (0 to 9)	0.5 (0 to 11)
CCIS, median (range)	16 (8 to 20)	8 (3 to 15)	10 (4 to 17)	10 (3 to 17)
CCIS: Cleveland Clinic Incontinence Score; FI: faecal incontinence.				

Table 3. Outcomes from Sorenson 2010

OUTCOME	ON PERIOD (1 month)	OFF PERIOD (1 month)
Incontinence episodes per week	0	0
Passive leakage per week, mean (95% CI)	0	0.43 (−0.41 to 1.27)
Soiling per week, mean (95% CI)	0.71 (−0.69 to 2.11)	1.86 (0.29 to 3.43)
CI: confidence interval.		

Table 4. Outcomes from Vaizey 2000

OUTCOME	ON PERIOD (2 weeks)	OFF PERIOD (2 weeks)
Incontinence episodes per week, mean (range)	1 (0 to 2)	12 (4 to 12)