Comparing treatments for adult faecal incontinence

SaFaRI:

Sacral nerve stimulation versus the **F**ENIX$_{TM}$ magnetic sphincter augmentation for **a**dult faecal incontinence: a **R**andomised **I**nvestigation

Chief Investigator: Prof David Jayne
Professor of Surgery
Section of Translational Anaesthesia and Surgery
Leeds Institute of Biological and Clinical Sciences
Level 7 Clinical Sciences Building
St James's University Hospital
Leeds LS9 7TF

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Key Contacts

Chief Investigator
Professor David Jayne
Professor of Surgery
Leeds Institute of Biological & Clinical Sciences
University of Leeds
Tel: 0113 206 5281
Fax: 0113 244 9168
Email: d.g.jayne@leeds.ac.uk

Trial Management
For queries regarding research site set-up and regulatory and governance issues, please contact

Miss Julie Croft
Senior Trial Manager
Clinical Trials Research Unit
University of Leeds
Tel: 0113 343 8394
Fax: 0113 343 4345
Email: j.croft@leeds.ac.uk

Ms Vicky Napp
CTRU Project Delivery Lead
Clinical Trials Research Unit
University of Leeds
Tel: 0113 343 1496
Fax: 0113 343 1471
Email: v.napp@leeds.ac.uk

Dr Fiona Collinson
Deputy Director Clinical Trials
Clinical Trials Research Unit
University of Leeds
Tel: 0113 343 1477
Fax: 0113 343 4345
Email: f.j.collinson@leeds.ac.uk

Data Management
For queries regarding eligibility, treatment, CRF and data query completion, safety reporting and randomisation process, please contact

Ms Vicky Liversedge
Data Manager
Clinical Trials Research Unit
University of Leeds
Tel: 0113 343 7998
Fax: 0113 343 6774
Email: V.Liversedge@leeds.ac.uk

Statistics
Mr Neil Corrigan
Senior Medical Statistician
Clinical Trials Research Unit
University of Leeds
Tel: 0113 343 1493
Fax: 0113 343 1471
Email: n.corrigan@leeds.ac.uk

Professor Julia Brown
Director of Clinical Trials Research Unit
Clinical Trials Research Unit
University of Leeds
Tel: 0113 343 1477
Fax: 0113 343 1471
Email: j.m.b.brown@leeds.ac.uk

Clinical Research Fellow
Miss Annabelle Williams
Clinical Research Fellow
Leeds Institute of Biomedical & Clinical Sciences
University of Leeds
Tel: 07966902249
Email: a.e.williams@leeds.ac.uk

Surgery
Mr Steve Brown
Reader in Surgery
Dept. of Colorectal Surgery
University of Sheffield
Tel: 0114 2714949
Email steven.brown@sth.nhs.uk

Ms Karen Nugent
Senior Lecturer in Surgery
Professorial Surgical Unit
University of Southampton
Tel: 0238 079 6145/7
Fax: 0238 079 4020
Email: kpn@soton.ac.uk

Mr Gregory Taylor
NIHR Clinical Lecturer (Academic Surgery)
Leeds Institute of Biomedical & Clinical Sciences (LIBACS)
University of Leeds
Tel: 0113 206 5280
Email: g.w.taylor@leeds.ac.uk

Mr Sushil Maslekar
Consultant Colorectal Surgeon
Leeds Teaching Hospital NHS Trust
Tel: 0113 243 3144
Email: Sushil.Maslekar@leedsth.nhs.uk

Health Economics
Professor Claire Hulme
Professor of Economics and Head of AUHE
Academic Unit of Health Economics (AUHE)
University of Leeds
Tel: 0113 343 0875
Email: c.t.hulme@leeds.ac.uk

Psychiatry
Dr David Protheroe
Consultant Liaison Psychiatrist
Leeds and York Partnership NHS Foundation Trust
Tel: 0113 392 3204
Fax: 0113 392 6771
Email: david.protheroe@nhs.net

Primary Care Advisors
Mrs Jen Lodge
Senior Community Incontinence Advisor
Leeds Primary Care Trust
Tel: 0113 305 5138
Fax: 0113 305 5138
Email: jen.lodge@nhs.net

Ms Debbie Beirne
Nurse Consultant
Leeds Institute of Cancer & Pathology (LICAP)
University of Leeds
Tel: 0113 206 7855
Email: d.a.beirne@leeds.ac.uk

Patient Advisor
Mr Adam Douglas

Randomisation – to randomise participants call:

Tel: 0113 343 4926

Safety reporting - to report Serious Complication (SCs) and Unexpected Serious Complication (USCs):

Tel: 0113 343 7998

Fax: 0113 343 6774

Contents

1 Study Summary

Study Title	**Sa**cral nerve stimulation versus the **F**ENIX$_{TM}$ magnetic sphincter augmentation for **a**dult faecal incontinence: a **R**andomised **I**nvestigation
Study Acronym	SaFaRI
Study Background	Faecal incontinence (FI) affects between 5% and 10% of the adult population. It is more common in females and with advancing age, and is the second most common cause of admission to a nursing home. It impacts on social, physical, and mental well-being and is a substantial and increasing burden on National Health Service (NHS) health resources.
Study Design	A prospective, UK multi-site, parallel-group, randomised clinical study investigating the safety and efficacy of the FENIX$_{TM}$ magnetic sphincter augmentation (MSA) for adult FI. The comparator is sacral nerve stimulation (SNS), a preferred treatment recommended by the National Institute for Health and Care Excellence (NICE) for the treatment of FI resistant to conservative therapies.
Study Objectives	The objectives of the study are to: i) determine the short-term safety and efficacy of FENIX$_{TM}$ MSA in adult FI. ii) assess FENIX$_{TM}$ MSA and SNS in terms of impact on Quality of Life (QoL) and cost effectiveness.
Study Endpoints	Primary endpoint: • Success, as defined by device in use and ≥ 50% improvement in the participant-reported Cleveland Clinic Incontinence Score (CCIS) at 18 months post-randomisation Secondary endpoints: • Safety of FENIX$_{TM}$ MSA or SNS, as judged by explant rates and operative and post-operative complications • Change in generic and disease-specific QoL • Cost-effectiveness
Study Population:	350 participants, aged ≥ 18 years, who have experienced moderate to severe FI symptoms (≥ 2 incontinent episodes per week) for more than 6 months and have failed conservative therapies. Participants must have an anal sphincter defect of less than 180° and be suitable and willing to undergo either SNS or FENIX$_{TM}$ MSA implantation.
Randomisation	Randomisation (1:1) to undergo either SNS or FENIX$_{TM}$ MSA. Randomisation to be performed by the Clinical Trials Research Unit (CTRU), Leeds.

Study Intervention:	SNS – this is a two-stage procedure whereby a temporary percutaneous electrode is used to stimulate the sacral nerves for a period of two weeks, after which the effect on continence is assessed and the electrode removed. If the response is positive (≥ 50% improvement in continence episodes), a permanent electrode and battery (Interstim II®) are implanted. Both temporary and permanent SNS are performed as day-case procedures. FENIX$_{TM}$ MSA implantation – is a minimally invasive surgical procedure whereby the FENIX$_{TM}$ MSA device is implanted, through a perineal incision, around the anal sphincter complex under radiological control. It typically involves a hospital stay of 1-3 days.
Duration:	All participants are followed-up to 18 months post-randomisation.
Evaluation of outcome measures	Participants are assessed 2 weeks post-operatively (temporary SNS, permanent SNS and FENIX$_{TM}$ MSA) and at 6, 12 and 18 months post-randomisation. QoL and participant-reported outcomes on incontinence and constipation symptoms are assessed using the CCIS, Obstructed Defecation score (OD-score) and Faecal Incontinence Quality of Life (FIQoL) along with the EQ-5D$_{TM}$ and SF-12® questionnaires. Adverse events and medical resources will be documented during study treatment and follow-up.

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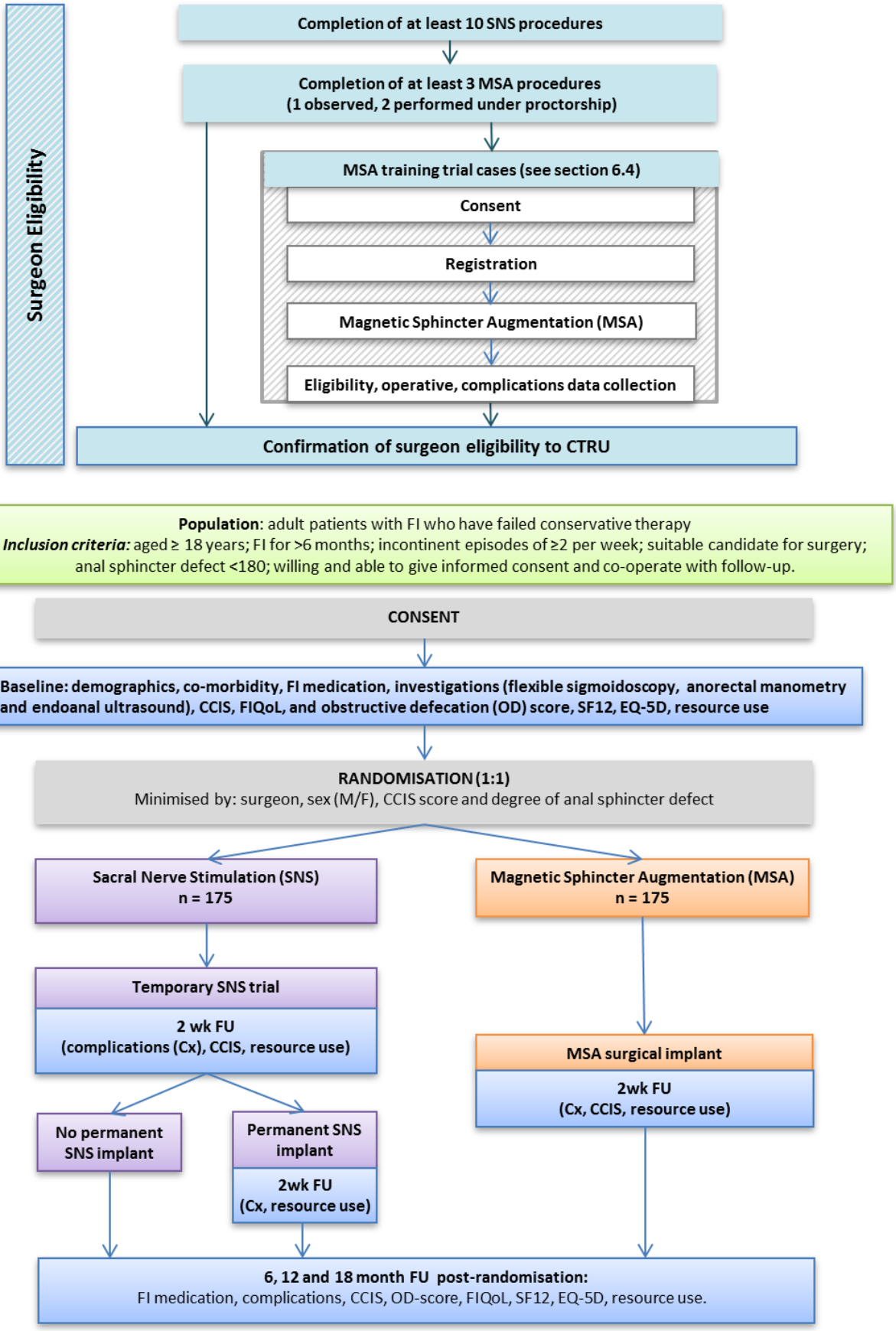
2 Study Schema



3 Background

Faecal incontinence (FI) is a distressing condition that affects between 5% and 10% of the adult population. It is more common in females and with advancing age, and is a particularly common problem in residential and nursing care homes, being the second most common cause of admission to a nursing home. It impacts on social, physical, and mental well-being and is a substantial burden on National Health Service (NHS) health resources.

3.1 Current Treatment Options

Current treatment strategies for adult FI are summarised in the National Institute for Health and Care Excellence (NICE) 2007 guidance. [i] All patients should undergo a thorough history and physical examination to determine the nature and severity of the problem and to identify a probable aetiological cause. Initial management consists of a combination of patient education, dietary modification, and anti-diarrhoeal medication. If this is unsuccessful, investigation in the form of endoscopic visualisation of the colorectum, anorectal manometry (pudendal nerve testing optional), and endoanal ultrasound is performed to further characterise the underlying disorder and inform treatment options.

3.1.1 Conservative Therapies

Conservative therapies include pelvic floor retraining, with or without biofeedback therapy, and irrigation techniques (rectal or antegrade irrigation). Biofeedback therapy aims to increase the patient's awareness of the muscles of continence and rectal sensation. Incontinent symptoms are improved in around 50% of patients, although there appears to be a significant placebo effect, with marked decrease in efficacy on long-term follow-up. [ii] Rectal irrigation, for example using the Peristeen® system (Coloplast, Denmark), aims to clear the rectum and lower colon of faecal residue. In the short-term it can have beneficial effects, but as a long-term solution patients frequently find it unacceptably time-consuming and inconvenient. Recently, there has been interest in the use of bulking agents to augment the anal sphincter. Data on efficacy is limited, but they may have a role controlling minor incontinence or "seepage", or where an isolated, sphincter defect is causing incomplete closure of the anal canal. [iii]

3.1.2 Surgical Interventions

Surgical interventions are indicated in those patients with moderate to severe FI that is resistant to the conservative therapies listed above.

3.1.2.1 Anterior sphincteroplasty, artificial bowel sphincter and dynamic graciloplasty

Anterior sphincteroplasty may be considered for patients with discrete sphincter defects, typically as a result of obstetric injury. Through a perineal incision the disrupted sphincter muscle is isolated and an overlapping sutured repair performed. Short-term results are reasonable, with some 70% of patients reporting an improvement in continence. However,

there is a drop-off in the longer term, with fewer than 50% of patients experiencing a benefit at 5-years. [iv] Patients who do worse following anterior sphincteroplasty include those with co-existent pudendal neuropathy, multiple sphincter defects or sphincter atrophy, and irritable bowel syndrome. Because of the poor long-term results, there has been a move away from sphincter repair, except in well-defined cases, and an increased enthusiasm for sacral nerve stimulation.

Another surgical intervention which may be considered to treat FI is the artificial bowel sphincter (ABS). The ABS consists of: (i) a fluid filled silicone cuff placed around the anus, (ii) a fluid filled, pressure regulating balloon positioned in the abdominal wall, and (iii) a manual pump connecting these components, placed in either the labia majora or the scrotum. When the cuff is inflated, the anal canal is sealed. The fluid is transferred to the balloon by the manual pump, deflating of the cuff and opening of the anal canal to allow defaecation. A successfully functioning device improves continence and quality of life. However, it is expensive, with the device alone costing around £4,000. The main problem with the ABS is the high complication rate. Revisional surgery is needed in between 12.5% and 50% of cases, with explantation rates between 16.7% and 41.2%. [v] The majority of revisions are for cuff leaks that are thought to arise from microperforations caused by repeated cycles of inflation and deflation over a number of years. Most explantations are for infective complications. As a consequence, the artificial bowel sphincter is not in common usage.

Dynamic graciloplasty involves mobilisation of the gracilis muscle from the inner thigh and wrapping around the anus to augment sphincter function. A neurostimulation device with an impulse generator is implanted to adapt the type II, fast-twitch muscle fibres to type I, slow twitch, fatigue-resistant fibres. The patient uses an external programming device to deactivate the electrical stimulation, relaxing the muscular contraction and enabling defaecation at a voluntary time. The success rate of the operation is between 40% and 60%. [vi] Like the ABS, the main problem is the high complication (infections 28%, device malfunction 15%, and leg pain 13%) and re-intervention rates. The use of dynamic graciloplasty in the UK has largely been superseded by sacral nerve stimulation.

3.1.2.2 Sacral Nerve Stimulation (SNS)

Sacral nerve stimulation (SNS) was first described for FI in 1995 [vii] and has grown in popularity, gaining NICE recognition as a minimally invasive treatment for moderate to severe FI. SNS works by a combination of anal sphincter augmentation and modulation of spinal/supra-spinal pathways. It benefits from a two-stage procedure, which enables the patient to assess acceptability and the clinician to evaluate efficacy prior to commitment to a permanent and expensive implant. An initial percutaneous nerve evaluation (PNE), or temporary stimulation, is performed under local, regional or general anaesthetic as a day-case procedure. A fine needle is inserted percutaneously into the sacral foramina (S3 or S4) on both sides to determine the best response in terms of anal sphincter contraction and dorsiflexion of the great toe (S3 stimulation). Once a satisfactory response is obtained, the temporary electrode is inserted, secured to the skin, and connected to an external test stimulator, allowing the patient to alter the stimulation voltage. The patient is asked to keep a bowel diary for the 2-3 weeks of stimulation, which allows the clinician to quantify the degree

of response. A positive response is defined as a reduction in incontinence episodes or incontinence score of ≥50% during the stimulation period.

Around 70% of patients have a good response and proceed to a permanent implant. Of these, 10% never gain any significant improvement and 26% experience loss of efficacy, usually within the first year. [viii] A further 2%-5% suffer irresolvable complications and undergo explantation. Thus, from a decision-to-treat, the long-term efficacy is around 45% to 50%. Overall, only 50% of patients thought to be eligible for SNS have a functioning device in the long-term.

The reasons for loss of efficacy are not clear, but may relate to device malfunction or fibrosis of the stimulating electrode leading to loss of conduction. Pain or discomfort at the stimulator site, down the leg, or into the vagina, is another commonly reported complication, experienced by 38.1% of patients. Overall, only 58.5% of patients who have a permanent implant have a good or acceptable result in the medium term.

Although SNS is a highly effective treatment for FI, it is also very costly. The component costs alone (excluding other direct and indirect medical costs) are £200 for the test stimulation and £9,393 for the permanent stimulator. [ix] A European study has calculated the 5-year cumulative costs for SNS at €22,150 per patient, which compared with €33,996 for a colostomy and €3,234 for conservative treatment. [x] Despite this, SNS has been shown to be cost-effective. The incremental cost-effectiveness ratio (ICER) for SNS is £25,070 per Quality Adjusted Life Year (QALY) gained, which is within the £30,000 per QALY threshold recommended by NICE as an effective use of NHS resources.

NICE first issued its guidance on SNS FI in 2004 [xi] and concluded that current evidence on safety and efficacy appeared to support its use but that the procedure should only be performed in specialist units by clinicians with a particular interest in the condition. A systematic review at that time included six case series and 266 patients. In patients who had permanent implants, complete continence was achieved in 41% to 75%, whereas 75% to 100% of patients experienced a decrease of 50% or more in the number of incontinent episodes. Improvements were noted in both disease-specific and general quality-of-life scores. The most recent review, including thirteen studies and 929 patients, has confirmed the short-term efficacy of SNS. [xii] Although the extent of the therapeutic effect varied between studies, a significantly beneficial effect was noted. Functional improvement was observed in 77% with idiopathic faecal incontinence, 76% in sphincter rupture/episiotomy, 78% after anal repair, and 73% after neurological injury. The benefit was not restricted to improved continence, with several studies showing a significant improvement in quality of life. [xiii]

3.1.2.3 FENIX$_{TM}$ Continence Restoration System (FENIX$_{TM}$ MSA)

The FENIX$_{TM}$ Continence Restoration System, or FENIX$_{TM}$ Magnetic Sphincter Augmentation (MSA), is a device that has been designed to reinforce the native sphincter for the treatment of FI resistant to conservative. It consists of a ring of 14 to 20 titanium beads with magnetic cores that are linked together to form an annular structure to be surgically placed around the anal sphincter complex. To defecate, the patient strains in a normal way and the force generated separates the beads to open the anal canal. Continence is restored by means of passive attraction of the beads. Once implanted, the device does not require patient input in order to function.

The FENIX$_{TM}$ MSA costs £4,000. Data on efficacy is limited, but suggests a ≥50% improvement in continence in 70% of patients. Complications can occur in around 20% of patients, leading to explantation in around 10%.

Preliminary results are promising with some 70% of patients reporting a benefit. But, studies have been small and a more rigorous evaluation is required prior to its widespread adoption.

The device is manufactured in different lengths to accommodate variations in anal canal circumference, and has been CE-marked since November 2011. FENIX$_{TM}$ MSA has been used in selected European and United States (US) centres to support a feasibility trial and was first used in the United Kingdom (UK) NHS in 2013.

The available evidence on safety and efficacy is limited but encouraging. Barussaud et al published on a series of 24 patients implanted with FENIX$_{TM}$ between 2008 and 2012. [xiv] All patients were female with a mean age of 64 years (range 35-78) with the mean duration of FI being 8.8 years (range 1-40). The mean follow-up was 17.6 months. There was one immediate post-operative complication, cardiac arrest due to drug intolerance. The patient recovered without further sequelae. Two patients (8.7%) were explanted, one for device separation, one for perineal abscess at 6 months post implant. Five patients (21%) were considered failures due to lack of improvement in FI symptoms. Bowel diary results showed a significant improvement in the number of weekly FI episodes decreasing from 32 to 8 in a 3 week diary. The mean Wexner (Cleveland Clinic Incontinence Score (CCIS)) score was reduced significantly from 16 at baseline to 7, 8 and 5 at 12, 24 and 36 months, respectively. All four domains of the Faecal Incontinence Quality of Life (FIQoL) questionnaire score significantly improved and remained stable post-operatively as compared to baseline.

A retrospective, case-matched comparison of the FENIX$_{TM}$ MSA with the artificial bowel sphincter (Acticon® Neosphincter) in 20 patients with severe FI [xv] showed that the FENIX$_{TM}$ MSA and ABS produced similar significant improvements in FI and quality of life (QoL). Compared to the artificial bowel sphincter, the FENIX$_{TM}$ MSA was associated with a significantly shorter operating time (FENIX$_{TM}$ MSA: 62 min vs ABS: 97.5 min, P 0.0273) and length of hospitalization (FENIX$_{TM}$ MSA: 4.5 days vs ABS: 10 days, P=0.001). No difference was observed in post-operative complications. The ABS was associated with more explants/revisions (FENIX$_{TM}$ MSA: 1 vs ABS 4, P=0.830), a greater incidence in post-operative constipation, and was more expensive.

Currently Torax® Medical, Inc.is conducting a post-market Registry in Europe. The FENIX$_{TM}$ MSA is not currently available in the US. The feasibility cohort is being followed out to five years post implant.

3.1.2.4 Permanent Stoma

For patients who fail the above surgical attempts to restore normal continence, the options are limited. A permanent stoma (usually colostomy) is often the last resort for patients with intractable FI. It is an effective strategy, but one that carries psychological and physical morbidity. Although most patients adapt to a permanent stoma, there is a continual fear of appliance leakage that can impact on social functioning. Around 50% of permanent stomas are complicated by parastomal herniation that may require surgical intervention. A stoma is also not a cheap intervention, with the 5-year cumulative costs estimated at £28,000. [xvi]

3.2 Rationale for current study

New technologies have often been introduced into clinical practice without rigorous evaluation of safety, efficacy and cost-effectiveness. Objective assessment has been overlooked due to the intrinsic appeal of new innovation, the need to be a part of a 'pioneering group', or worse, due to the financial incentives from industry. Once introduced, low grade observational evidence is often used to keep practices going. As a result, it has often been easier to "stop them starting" than to "start them stopping". [xvii] Ideally, any new technology introduced into clinical practice should be simultaneously evaluated, and in most cases the best way of doing this is by randomised comparison with an already established technique.

The National Institute for Health Research Horizon Scanning Centre (NIHR HSC) was established to "supply timely information to key health policy and decision-makers within the NHS about emerging health technologies that may have a significant impact on patients or the provision of health services in the near future". In May 2012 the NIHR HSC reported on the FENIX$_{TM}$ Continence Restoration System (FENIX$_{TM}$ MSA) and concluded "in order to determine its potential place in the pathway of care for FI larger long term studies of the safety, effectiveness and cost-effectiveness of FENIX$_{TM}$ in comparison to existing treatments are needed". [xviii] Thus, although FENIX$_{TM}$ MSA might have a role to play in the treatment of FI, the evidence is not robust enough to support widespread adoption.

A unique opportunity presents itself; it will be possible to undertake a rigorous, prospective assessment of the new FENIX$_{TM}$ MSA as it is adopted into the NHS. Reliable data, collected independently from commercial interests, will be made available on the safety and efficacy of the device. This will include information on safety, efficacy, QoL and health economics. Important information will be gained on the costs associated with the device, enabling the incremental cost-effectiveness ratio per QALYs to be determined. This will allow healthcare providers to make informed decisions about value for money and future provision of the technology.

Sacral nerve stimulation has been chosen as the comparator to FENIX$_{TM}$ MSA. This is because SNS is now the preferred, and NICE recommended surgical intervention for FI resistant to conservative therapies; the NIHR HSC report from May 2012 also identified SNS as the preferred comparator for any randomised comparison with FENIX$_{TM}$ MSA. Additional, important data will be collected about SNS. SNS is a costly yet highly effective treatment for FI. However, concerns have been expressed about the lack of efficacy when analysed on an intention-to-treat basis and the loss of efficacy on longer-term follow-up. This study will provide an additional opportunity to better clarify the indications for SNS and the indicators of success.

We will also be able to comprehensively document, for the first time, the treatment and associated costs for patients who fail either SNS or FENIX$_{TM}$ MSA. In effect, these patients will provide comparative, longitudinal data of the patient pathway where FENIX$_{TM}$ MSA or SNS is either not suitable or not available.

In addition to the costs detailed above, the health economics will provide data on the short and long term cost effectiveness of FENIX$_{TM}$ MSA vs. SNS. Within the analyses use of two measures of health related quality of life to produce QALYs, the SF-12® together with the EQ-5D$_{TM}$, will allow assessment of the sensitivity of the EQ-5D$_{TM}$ to detect changes in FI which is to date unproven. The disease-specific questionnaire chosen to assess QoL, the

FIQoL, collects important information on many social and psychological aspects of FI (shame, depression, enjoyment, etc.). These aspects of FI have received little previous recognition in the literature and remain poorly defined. We have included a Consultant Liaison Psychiatrist with an interest in gastrointestinal dysfunction in our study team to help analysis of these important components. This will provide an invaluable insight into the mental health issues associated with FI.

4 Aims and Objectives

The overall objectives of the study are to:

i) determine the short-term safety and efficacy of FENIX$_{TM}$ MSA and SNS in adult FI.

ii) assess FENIX$_{TM}$ MSA and SNS in terms of impact on QoL and cost effectiveness.

Aims:

The study will involve a thorough evaluation of the FENIX$_{TM}$ MSA device, as compared to SNS, for the treatment of adult FI.

Primary outcome measure:

Success, as defined by device in use and ≥ 50% improvement in the participant-reported Cleveland Clinic Incontinence Score (CCIS) at 18 months post-randomisation Secondary outcome measures:

- length of hospital stay
- complications,
- re-interventions
- constipation
- quality of life
- cost effectiveness

Outcomes of the study will inform clinicians, healthcare providers, and the public and patients about the relative merits of the two interventions.

5 Design

This is a UK multi-site, prospective, parallel-group, randomised controlled, unblinded study to evaluate the safety and efficacy of the FENIX$_{TM}$ MSA for moderate to severe adult FI as compared to SNS, a NICE recommended treatment for FI resistant to conservative therapies. [xix] 350 participants will be randomised on an equal basis to either FENIX$_{TM}$ MSA

or SNS implants. The follow-up period finishes 18 months after the last participant is randomised.

The study will not be blinded to participants, medical staff, or clinical trial staff, given the difference between the two devices being compared (SNS treatment requires a temporary implant followed by a permanent implant if successful and involves patient input to function).

6 Eligibility

6.1 Patient eligibility

FI is defined as the inability to control the passage of faeces through the anus. For inclusion in the study, conservative treatments should have been tried and proven to be ineffective. Patients should have moderate to severe FI, defined as suffering incontinence for more than 6 months, and suffering 2 or more incontinent episodes per week, and be suitable and willing to undergo either SNS or FENIX$_{TM}$ MSA implantation.

Both the technology under evaluation (FENIX$_{TM}$ MSA) and the comparator (SNS) will be evaluated on the same patient population. Incontinence may be from any aetiology, including anal sphincter injury and neurological disorders.

6.1.1 Inclusion and exclusion

Eligibility waivers to inclusion or exclusion criteria are not permitted.

6.1.1.1 Inclusion criteria

1. Aged ≥ 18 years
2. Able to provide written informed consent
3. FI for more than 6 months
4. Incontinent episodes of ≥ 2 per week
5. Suitable candidate for surgery, as judged by the operating surgeon[1]
6. Suitable for either FENIX$_{TM}$ MSA or SNS *(Unless the patient is being registered as a **Training case**, in which case they need only be suitable for the FENIX$_{TM}$ MSA)*
7. Anal sphincter defect < 180° as documented on endoanal ultrasound scan
8. Able and willing to comply with the terms of the protocol including QoL questionnaires

[1] Suitability assessment includes general fitness and conservative treatments for FI having proved ineffective.

6.1.1.2 Exclusion criteria

1. Previous interventions for FI i.e. SNS, FENIX$_{TM}$ MSA or ABS *(Unless the patient is being registered as a **Training case**, in which case they can have had previous interventions for FI)*
2. Chronic gastrointestinal motility disorders causing incontinence due to diarrhoea
3. Obstructed defaecation, as defined by an inability to satisfactorily evacuate the rectum (*we recommend that the Obstructed Defecation score(OD-score) is calculated and is ≤8 for trial inclusion)*
4. Anal sphincter defect ≥ 180°, as documented on endoanal ultrasound scan
5. An electric or metallic implant within 10cm of anal canal
6. Co-existent systemic disease (e.g. scleroderma, etc.) impacting on continence
7. Active anorectal sepsis
8. Diagnosis of colorectal or anal cancer within 2 years
9. External rectal prolapse
10. Significant scarring of the anorectum that, as judged by the treating surgeon, would prohibit FENIX$_{TM}$ MSA implantation or put the patient at high risk of implant erosion
11. Pregnancy[2]
12. Immunocompromise, including haematological abnormalities and treatment with steroids or other immunomodulatory medicines.
13. Congenital spinal abnormalities, preventing SNS implantation
14. Known requirement for future Magnetic Resonance Imaging (MRI) surveillance, which would be contraindicated in the presence of metallic implant
15. Suspected or known allergies to titanium

6.1.1.3 Concurrent clinical trials

Participants will not be eligible for entry into other clinical trials of surgical technique. However patients will be suitable for inclusion in SaFaRI if they have already participated in a previous non-surgical trial. Please contact the Clinical Trials Research Unit (CTRU, University of Leeds) for further clarification.

6.2 Research site eligibility

The study will open in at least 20 research sites throughout the UK. Each site must fulfil a set of pre-specified criteria and complete a registration form which verifies that the research site is willing and able to comply with the study requirements. This will be signed by the proposed local Principal Investigator (PI) on behalf of all staff who will be affiliated with the study. Research sites will be required to obtain local management approval, return all required essential documentation to CTRU and undertake a site initiation with the CTRU prior to the start of recruitment into the study.

Participation of research sites will be dependent upon the following criteria:

[2] It is the local surgeon's responsibility to ensure this is assessed in women of child-bearing potential according to local standard of care

1. Site must be an NHS hospital providing specialist treatment for adult FI with at least one participating surgeon holding membership of The Association of Coloproctology of Great Britain and Ireland (ACPGB&I)
2. Site must have experience in the provision of SNS
3. Site must have the facilities to perform visualisation of the colorectum (flexible sigmoidoscopy as a minimum), anorectal manometry (pudendal nerve testing optional), and endoanal ultrasound.

6.3 Surgeon Eligibility

Prior to randomising patients, all participating surgeons must have experience of a minimum of 10 SNS implantations and a minimum of 1 observed FENIX$_{TM}$ MSA procedure and 2 FENIX$_{TM}$ MSA procedures under proctorship. Surgeons must be aware of the standard technique for FENIX$_{TM}$ MSA implantation as demonstrated in the SaFaRI study procedure video. A registration stage is included for surgeons without FENIX$_{TM}$ MSA experience (see section 6.4).

Participating surgeons must also provide the total number of FENIX$_{TM}$ MSA or SNS implantations they have performed upon starting the study, and periodic information on the total number of FENIX$_{TM}$ MSA or SNS implantations they perform during the studyperiod.

6.4 Registration for FENIX$_{TM}$ MSA Training Cases

Prior to randomising patients into the study, surgeons are required to have observed at least 1 implantation and performed 2 implantations under proctorship (see section 6.3 above). Surgeons who have this experience prior to study participation can proceed immediately to the randomisation phase (see section 7.2 below). Surgeons who have not had this experience before study participation will join the registration phase of the study whereby the first 2 eligible (please refer to section 6.1.1.) patients providing consent will be registered to the study and receive FENIX$_{TM}$ MSA implants (there will be no randomisation in the registration phase). These 2 operations performed under proctorship will be considered study training cases and will not be included in the main study. These patients will be registered as described in section 6.4.2. The surgeon may then start the randomised phase.

6.4.1 Timing of registration of FENIX$_{TM}$ MSA training cases

A verbal explanation of the registration part of the study along with the approved Patient Information Sheet (PIS)/Informed Consent Form (ICF) for registration cases will be provided by a medically qualified member of the healthcare team for the patient to consider. The PIS will provide detailed information about the rationale, design and personal implications of the study.

Patients will be given as much time as necessary to consider their participation in the study; the right of the patient to refuse consent without giving reasons will be respected.

Assenting patients will then be invited to provide informed, written consent for their participation in the study, including explicit consent for the transfer of a copy of their signed consent form to the CTRU.

Informed consent may only be obtained by the PI or an appropriate healthcare professional. The healthcare professional must have knowledge of the study interventions and have received training in the principles of Good Clinical Practice (GCP) and the Declaration of Helsinki 1996. He/she must be fully trained in the study according to the ethically approved protocol and be authorised and approved by the PI to take informed consent as documented in the study Authorised Personnel Log (APL). The PI retains overall responsibility for the informed consent of participants at their research site.

The patient consent form with all original signatures must be retained in the Investigator Site File (ISF). A copy of the signed consent form must be given to the participant, and a record of the consent process, detailing the date of consent and witnesses, must also be kept in the participant's medical notes (this may include a copy of the consent form as per local practice). A copy of the signed consent form must also be transferred to the CTRU.

Participants will remain free to withdraw from the study at any time by revoking consent without giving reasons and without prejudicing any further treatment.

Participants must be registered as soon as possible after consent is obtained. The interval between registration and surgery must be kept to a minimum, and wherever possible should not exceed 6-weeks.

6.4.2 Registration process

Informed written consent for entry into the study, and baseline investigations (examination of the colorectum, anorectal manometry and endoanal ultrasound) must be obtained prior to registration. Following confirmation of written informed consent and eligibility, participants will be registered into the study by an authorised member of staff at the research site. Registration will be performed centrally using the CTRU automated 24-hour registration/randomisation telephone service. Authorisation codes and personal identification numbers (PINs), provided by the CTRU, will be required to access the registration/randomisation telephone service.

Please complete the Registration Form prior to calling the 24-hour registration/randomisation telephone service. The following information will be required at registration:

- Participant details, including initials and date of birth
- Name and code of the research site
- Name of treating surgeon
- Name of the person making the registration
- Confirmation of eligibility
- Confirmation of written informed consent

The registration phone call will allocate participants a unique 5 digit study number. All participants in the registration phase will receive FENIX$_{TM}$ MSA surgery.

6.4.3 Data Collection

The following data will be collected for registered participants:

- Eligibility
- Operative data
- Complications occurring up to 30 days post operation

7 Recruitment Process

7.1 Recruitment Setting

Participants will be recruited from NHS hospitals providing a specialist FI service, with membership of the ACPGB&I and experience in SNS. A study summary sheet will be produced which will give an overview of clinical research, and an introduction to the rationale, design, and personal implications of the study. This study summary sheet will be available for community sources to give to potential participants at the point of referral to the acute setting.

A total of 350 participants (175 in each arm) will be recruited into the study over a 30-month period. Research site set-up and recruitment of participants will be reviewed approximately 12 months from opening.

7.1.1 Eligibility Screening

Participating research sites will be required to complete a log of all patients screened for eligibility who are not randomised either because they are ineligible or because they decline participation. Anonymised information will be collected including:

- Age
- Gender
- Ethnicity
- Date screened
- Reason not eligible for study participation, or
- Eligible but declined and reason for this, or
- Other reason for non-randomisation

This information will be requested from research sites on a regular basis (at least 3 monthly) by the CTRU.

7.1.2 Informed Consent

Patients will be approached for possible recruitment following investigations, as per institutional policy for FI, but which must include visualisation of the colorectum (flexible sigmoidoscopy as a minimum), anorectal manometry (pudendal nerve testing optional), and endoanal ultrasound. Suitability for inclusion into the study will be assessed (see section 6.1) and patients will be provided with verbal and written details. A verbal explanation of the study along with the approved PIS/ ICF will be provided by a medically qualified member of the healthcare team for the patient to consider. The PIS will provide detailed information about the rationale, design and personal implications of the study.

Following information provision, patients must be given the opportunity to discuss the study with their family and healthcare professionals before they are asked whether they would be willing to take part in the study. Patients will be given as much time as possible to consider their participation in the study; ideally they will be allowed 24 hours as a minimum. The right of the patient to refuse consent without giving reasons will be respected.

Assenting patients will then be formally assessed for eligibility and invited to provide informed, written consent for their participation in the study, including explicit consent for the transfer of a copy of their signed consent form to the CTRU.

Informed consent may only be obtained by the PI or an appropriate healthcare professional. The healthcare professional must have knowledge of the study interventions and have received training in the principles of GCP and the Declaration of Helsinki 1996. He/she must be fully trained in the study according to the ethically approved protocol and be authorised and approved by the PI to take informed consent as documented in the study APL. The PI retains overall responsibility for the informed consent of participants at their research site.

The patient consent form with all original signatures must be retained in the ISF. A copy of the signed consent form must be given to the participant, and a record of the consent process, detailing the date of consent and witnesses, must also be kept in the participant's medical notes (this may include a copy of the consent form as per local practice). A copy of the signed consent form must also be transferred to the CTRU.

Participants will remain free to withdraw from the study at any time by revoking consent without giving reasons and without prejudicing any further treatment.

7.1.3 Loss of Capacity Following Informed Consent

7.1.3.1 Participants recruited in England/Wales

Loss of mental capacity of a participant after giving informed consent for the study is expected to be a rare occurrence. Nevertheless, in such an eventuality consent for the participant's continued participation will be sought from a Consultee in accordance with the Mental Capacity Act 2005 (MCA) for participants recruited in England or Wales.

Where the Consultee consents to the participant's continued participation, the participant will not receive any further study-specific interventions, but safety data and follow-up data via will be collected from their medical records by their clinical healthcare team.

It will be assumed that participants have capacity until it is shown to be absent. For those lacking capacity, a Personal Consultee / Nominated Consultee, as defined in the MCA, will be identified, respecting principles of confidentiality, by:

- Asking the participant (and if necessary confirming this with ward staff (before approaching the Consultee)
- If the participant is unable to identify a Personal Consultee, the clinical care team will be requested to identify an appropriate potential Personal Consultee. The Personal Consultee will usually be a relative or non-paid carer involved in the care of the participant.
- The clinical care team will also check with ward staff whether the participant has made an Advance Directive relevant to identifying a Personal Consultee and act in accordance with this.

Where a potential Personal Consultee can be identified, he/she will initially be contacted by telephone if face-to-face communication is not possible. The Personal Consultee will be advised that they need to put their own views aside and make a declaration based on the likely views of the participant with regard to continuing to take part in the study. Details of how this will be recorded are given below.

If there is no response of the potential Personal Consultee, or the Personal Consultee is unwilling to act, an appropriate member of the hospital staff who has no connection with the research project will be asked to act as the Nominated Consultee. The Nominated Consultee will also be advised that they should make a declaration taking into consideration the likely views of the participant, setting aside their own views. If the Nominated Consultee advises that the participant may continue participation in the study, a letter will be sent to the potential Personal Consultee informing them that the participant has been enrolled for continued participation in the study and requesting them to inform the ward staff or the research team if they have any concerns.

If the Personal or Nominated Consultee agree to the participant's continued participation in the study, this will be confirmed via a signed Consultee declaration form. The original Consultee Declaration Form will be retained alongside the partiicipant's original consent in the investigator site file. A copy of the Consultee Declaration Form will be given to the Consultee, one sent to the participant's GP and one to the CTRU

7.1.3.2 Participants recruited in Scotland

Loss of capacity of a participant after giving informed consent for the trial is expected to be a rare occurrence. Nevertheless, explicit prospective consent will be sought from all participants recruited in Scotland to allow for the continued collection of safety and follow-up data via their clinical care team in such an eventuality. In the event of incapacity, participants will not receive any further study-specific interventions

7.2 Randomisation (for eligible surgeons)

For the majority of surgeons it is anticipated they will commence randomisations following the registration of two participants to the registration phase of the study (see section 6.4). Surgeons completing the minimum required cases prior to study participation may commence straight to randomisation once confirmation of this has been provided to CTRU. In either case, surgeon eligibility to commence the randomisation phase will be confirmed by the CTRU and the surgeon will be given access to the randomisation section of the 24hour registration/randomisation telephone service.

7.2.1 Timing of randomisation

It is anticipated that there may be a variable delay between obtaining participant consent for inclusion in the study and randomisation and first surgery, dependent on individual hospital waiting lists for elective benign surgery. Ideally, randomisation and first surgery take place as soon as possible after consent is obtained and after participants have completed their baseline participant-completed questionnaires (see section 9.2). The interval between randomisation and surgery must be kept to a minimum, and wherever possible should not exceed 6-weeks to minimise inaccurate data collection due to a change in the participant's condition. Baseline participant-completed questionnaires must be collected immediately prior to randomisation to avoid bias in questionnaires occurring due to patient knowledge of randomisation allocation.

7.2.2 Randomisation process

Informed written consent for entry into the study, baseline investigations (examination of the colorectum, anorectal manometry and endoanal ultrasound) and participant-completed questionnaires (EQ-5D$_{TM}$, SF-12®, CCIS, FIQoL and OD-score - see section 11.0 0) should wherever possible be completed prior to randomisation, however where this is not possible, these must be completed prior to the participant being made aware of their randomised operation (FENIX$_{TM}$ MSA or SNS). Following confirmation of written informed consent and eligibility, participants will be randomised into the study by an authorised member of staff at the research site. Randomisation will be performed centrally using the CTRU automated 24-hour registration/randomisation telephone service. Authorisation codes and PINs, provided by the CTRU, will be required to access the 24-hour registration/randomisation telephone service.

Please complete the Randomisation Form prior to calling the 24-hour registration/randomisation telephone service. The following information will be required at randomisation:

- Participant details, including initials and date of birth
- Name and code of the research site
- Name of the person making the randomisation

- Confirmation of eligibility
- Confirmation of written informed consent
- Stratification factors (see section 7.2.3)

The randomisation phone call will allocate participants a unique 5 digit study number and inform of the randomised operation for that participant (FENIX$_{TM}$ MSA or SNS).

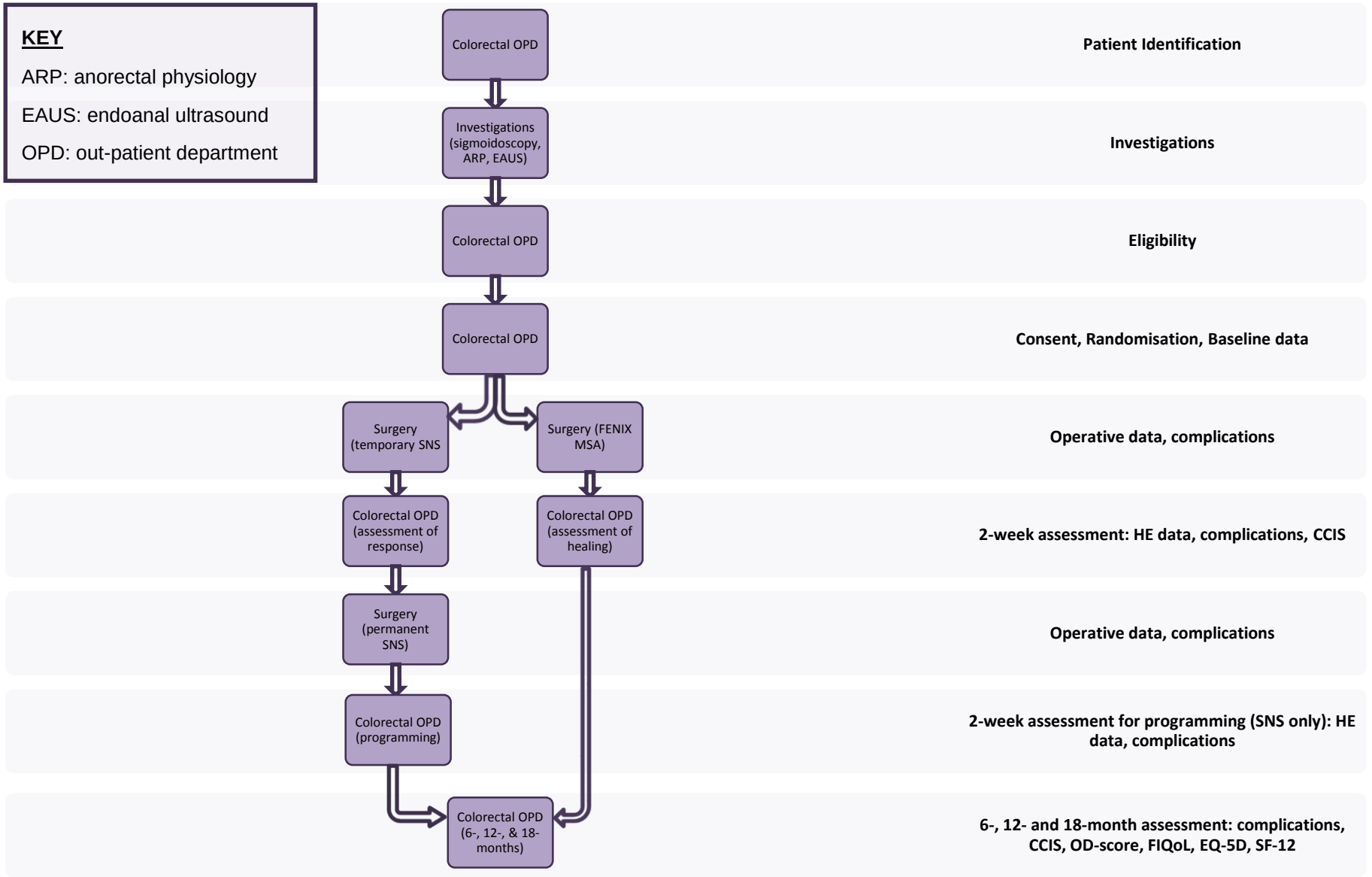
24 hr direct line for randomisation: 0113 343 4926

7.2.3 Treatment allocation

Participants will be randomised on a 1:1 basis to receive either FENIX$_{TM}$ MSA or SNS and will be allocated a unique study number. A computer-generated minimisation programme that incorporates a random element will be used to ensure treatment groups are well-balanced for the following participant characteristics, details of which will be required for randomisation:

- Treating surgeon
- Participant gender (male or female)
- Severity of incontinence (CCIS)
    - Mild to moderate: CCIS score ≤ 10
    - Moderate to severe: CCIS score > 10
- Degree of anal sphincter defect on endoanal ultrasound
    - No anal sphincter defect
    - Anal sphincter defect ≤ 90degrees
    - > 90 degrees anal sphincter defect <180 degrees

8 Intervention Details


KEY
ARP: anorectal physiology
EAUS: endoanal ultrasound
OPD: out-patient department
Colorectal OPD
Patient Identification
Investigations (sigmoidoscopy, ARP, EAUS)
Investigations
Colorectal OPD
Eligibility
Colorectal OPD
Consent, Randomisation, Baseline data
Surgery (temporary SNS
Surgery (FENIX MSA)
Operative data, complications
Colorectal OPD (assessment of response)
Colorectal OPD (assessment of healing)
2-week assessment: HE data, complications, CCIS
Surgery (permanent SNS)
Operative data, complications
Colorectal OPD (programming)
2-week assessment for programming (SNS only): HE data, complications
Colorectal OPD (6-, 12-, & 18-months)
6-, 12- and 18-month assessment: complications, CCIS, OD-score, FIQoL, EQ-5D, SF-12

8.1 Pre-operative investigations and preparation (SNS and FENIX$_{TM}$ MSA)

Pre-operative investigation and preparation will be as per institutional protocol, which must include as standard practice visualisation of the colorectum (flexible sigmoidoscopy as a minimum), anorectal manometry (pudendal nerve testing optional), and endoanal ultrasound.[3]

8.2 Device Implantation and Post-operative care assessments

8.2.1 SNS

SNS implantation will be performed in accordance with each research site's usual practice. SNS implantation is a two-stage procedure. A temporary device is implanted during a day-case procedure and the degree of response to the device is recorded by the participant over the course of two weeks. Response should be assessed in accordance with each research site's usual practice. Please note that CCIS score will be recorded for study purposes regardless of how response is assessed locally.

If the response is positive (defined as a ≥50% improvement in incontinence episodes or ≥50% improvement in CCIS score) a second day-case procedure is scheduled and a permanent SNS device is implanted.

If the response is negative, the temporary device is removed and the participant does not receive any further study intervention but will continue follow-up for the required 18-month period. Further treatment will be as per current standard practice but participants will not be permitted to undergo FENIX$_{TM}$ MSA implantation during the 18-month follow-up period post-randomisation.

Post-operative care will be as per standard practice, but participants must be reviewed at clinic 2 weeks post-operatively for both temporary and permanent device implants, and at 6, 12 and 18 months post-randomisation as a minimum. Any further visits will be according to local standard clinical practice, but will be captured on the follow-up Case Report Form (CRFs).

8.2.2 FENIX$_{TM}$ MSA

FENIX$_{TM}$ MSA implantation will be performed during an in-patient stay (usually 1-3 days).Participants failing FENIX$_{TM}$ MSA will not be permitted to undergo SNS during the 18-month follow-up period.

In accordance with the manufacturer's recommendations, participants implanted with the FENIX$_{TM}$ MSA will be provided with laxatives/stool softeners and analgesics, in line with clinician preference, for a period of 7-10 days. No post-operative care is required above routine wound-care, but participants must be reviewed at 2 weeks post-operatively and at 6,

[3] These investigations if used to determine eligibility do not need to be repeated at baseline for study purposes.

12 and 18 months post-randomisation as a minimum. Any further visits will be according to local standard clinical practice and will be recorded on the follow-up CRFs.

8.2.2.1 Supply

FENIX$_{TM}$ MSA devices will be provided at a discounted cost by the manufacturer Torax® Medical, Inc. Kits of 7 differently sized devices will be provided to each research site by Torax® Medical, Inc. and will remain the property of Torax® Medical, Inc. Once a device is successfully implanted, the research site will be invoiced by Torax® Medical, Inc for the successfully implanted device at the agreed discounted cost.

Appropriate procedures must be in place at site to ensure a smooth supply chain.

8.2.3 Device Failure

Should a participant experience device failure which requires explantation, they will not be permitted to undergo implantation of the alternative study intervention during the 18-month follow-up period post-randomisation.

The literature on SNS, combined with personal experience, suggests that around 30% of participants who undergo a trial of temporary SNS will not have a positive response and will not progress to a permanent implant. This cohort of patients is difficult to treat due to the lack of current alternative therapies. They are at the end-of-the-line of current treatment modalities. Within the study setting, they will be treated according to current practice, i.e. the choices available to them are reversion to best medical treatment with continent aids for symptom control or they will be offered the option of a permanent stoma.

Participants who fail temporary SNS or suffer a lack of efficacy with permanent SNS (failure to reproduce the positive result of temporary stimulation) will not be permitted to undergo FENIX$_{TM}$ MSA implantation within their 18-month post-randomisation follow-up period. In reality, this should not present too much of a clinical or ethical problem. In patients who have failed temporary SNS a further period of conservative management is often tried before proceeding directly to another surgical intervention. For patients in whom there is difficulty establishing efficacy of a permanent SNS implant, exhaustive attempts are undertaken to re-programme the device before it is deemed to be ineffective, which can take several months.

Similarly, patients in whom the FENIX$_{TM}$ MSA fails and is explanted will not be treated with SNS within their 18-month post-randomisation follow-up period, to enable collection of outcome and cost effectiveness data relating to device failure.

In both groups of patients, an 18-month post-randomisation wait prior to implantation of a FENIX$_{TM}$ MSA or SNS will not add significantly to that which would have occurred outside of the clinical trial setting.

8.2.4 Schedule of Clinical Assessments

The timing of clinical assessments are summarised in Table 1. All participants will be followed up via clinic visits as per protocol until 18 months post-randomisation.

Table 1: Schedule of Events

	Baseline	Operative (temp SNS & FENIX$_{TM}$ MSA)	2 week Post-operative Review[4] (temp SNS & FENIX$_{TM}$ MSA)	Operative (permanent SNS)	2 week Post-operative Review[4] (permanent SNS)	6[5,6], 12 & 18 months Post-randomisation Assessment
Clinical examination[1]	√		√		√	√
Operative details[2]		√		√		
Complications[3]		√	√	√	√	√
Resource usage	√	√	√	√	√	√

[1] At baseline this includes data collection on demographics, co-morbidity, results of investigations (flexible sigmoidoscopy, anorectal manometry and endoanal ultrasound).

[2] Including recording of concomitant medications relevant to bowel function.

[3] For device-related complications refer to sections 10.2.2 and 10.2.3.

[4] For the Post-operative Review following the temporary SNS implant, this visit must be no longer than 21 days later.

[5] If the scheduled 6-month Post-randomisation Assessment visit is ≤ 28days after a Post-operative Review visit, then this visit can be omitted; if it is scheduled 29 days or more afterwards, it should proceed as planned.

[6] If the participant is unable to attend the 6 month visit in clinic, this assessment may take place over the telephone.

9 Data Collection

Participating research sites will be expected to maintain a file of essential study documentation (ISF), which will be provided by the CTRU, and keep copies of all completed CRFs for the study. The CRFs and participant-completed questionnaires will contain the participant's unique study number, date of birth, and initials. Clinical data will be collected at baseline, surgery, 2-weeks post-operatively, and at 6, 12 and 18 months post-randomisation; participant-completed data will be collected at baseline, 2-weeks post-operatively and at 6-, 12- and 18-months post-randomisation.

9.1 Submission of Study Data

Participating research sites will record study participant data on study-specific paper CRFs and submit them to the CTRU. Missing and discrepant data will be flagged and additional data validations raised as appropriate from the CTRU data management team.

9.2 Pre-operative Assessments and Data Collection

Participants must be screened, assessed for eligibility and have provided written informed consent before they can then be randomised (Section 7.2)

Data collected on the pre-operative CRFs (Eligibility Checklist, Baseline and Randomisation Forms) will include (but will not be limited to):

- Personal details and demographics including height, weight, gender, and American Society of Anesthesiologists (ASA) grade
- Results of pre-operative investigations: flexible sigmoidoscopy, anorectal manometry and endoanal ultrasound to confirm eligibility
- Known co-morbidities
- Concomitant medications relevant to bowel function
- Planned operation (FENIX$_{TM}$ MSA, SNS)
- Other information required to confirm eligibility

Following written informed consent and wherever possible prior to randomisation (where this is not possible this must be prior to the participant being made aware of their randomised operation) participants will also be asked to complete the baseline participant-completed questionnaires:

- CCIS
- OD-score
- FIQoL
- EQ-5D$_{TM}$

- SF-12®
- Health and Social Care Resource Use

9.3 Operative Data Collection

An operative CRF will be completed. This will collate data relating to the operation including (but not limited to):

- Surgeon
- Performed operation (FENIX$_{TM}$ MSA, temporary or permanent SNS)
- Duration of operation
- Duration of hospital stay
- Any intra-operative complications, including device-related complications

9.4 Post-operative Data Collection

Post-operative care will be as per institutional protocol. However, a Post-operative Review visit must be scheduled ≥ 14 days after surgery and as close to this date as possible.

For participants randomised to receive the SNS implant the temporary SNS device will be removed at 2 weeks and an assessment made whether to progress to a permanent implant based on ≥50% improvement in incontinence episodes or ≥50% improvement in CCIS score. For those who go on to have a permanent implant, there will be two Post-operative Review visits, the first after the temporary implant and the second after the permanent implant. For the Post-operative Review following the temporary SNS implant, this visit must be no longer than 21 days from the surgery date

Data collected will include:

- Duration of post-operative hospital stay
- Post-operative complications and severity, including device-related complications
- Details of any further referrals or surgery required and reason
- CCIS score
- Details of health resource use, including take-home medications relevant to bowel function

Participants will also complete participant-completed questionnaire CCIS following the temporary SNS implantation or FENIX$_{TM}$ MSA (see section 11.0 below).

9.5 Follow-up Data Collection

9.5.1 Data Collection for clinical assessments

At 6[4][5], 12 and 18 months from randomisation, a clinical assessment must be carried out for all participants.

Data collected will include (but will not be limited to):

- Confirmation that device is in situ and in use
- Post-operative complications and severity, including device-related complications
- CCIS score

9.5.2 Data Collection for participant-completed questionnaires

Participant-completed questionnaires will be posted out to participants for completion at 6, 12 and 18 months post-randomisation (see section 11.0 below). Wherever possible, these patient-completed questionnaires must be completed at 6, 12 and 18 months post-randomisation, +/- 2 weeks.

9.6 Pregnancy

Any suspected or confirmed pregnancies between the date of randomisation to the date of surgery must be reported to the CTRU **within 7 days** of the research site becoming aware. All further protocolised treatment must be stopped immediately if a pregnancy occurs or is suspected during this time; it is the responsibility of the treating surgeon to decide what course of action should be taken in relation to ensuring the participant's ongoing treatment outside of the study protocol.

The CTRU will inform the Sponsor of all reported pregnancies.

9.7 Death

All deaths must be recorded on the Notification of Death CRF. Data collected will include (but will not be limited to):

- Date of death
- Cause of death

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[4] If the scheduled 6-month post-randomisation visit is ⩽ 28days after the post-operative review visit, then this visit can be omitted; if it is scheduled 29 days or more afterwards, it should proceed as planned.

[5] If the participant is unable to attend the 6 month visit in clinic, this assessment may take place over the telephone.

Deaths occurring in the study population from the date of consent to 18 months post - randomisation must be reported on the Notification of Death CRF. If a participant dies within 6 months of surgery, a completed Notification of Death CRF must be faxed **within 7 days** of site becoming aware of the event. The original form must then be posted to the CTRU and a copy retained at the research site. If a participant dies more than 6 months after their operation then a completed Notification of Death CRF will be collected with follow-up data and returned with the 6-, 12- or 18-month follow-up CRFs to the CTRU (see section 9.5).

9.8 Withdrawal

In line with usual clinical care, cessation or alteration of treatment at any time will be at the discretion of the attending clinician or the participant themselves.

In the event that a participant withdraws prior to randomisation, no further data is required to be submitted.

In the event that a participant withdraws after randomisation but prior to surgery, collection of follow-up data will still be required

For participants withdrawing from the study after surgery, they will still attend follow-up visits unless unwilling to do so and safety data and follow-up data will continue to be collected.

If a participant explicitly states they do not wish to contribute further data to the study or to complete any further participant questionnaires, the CTRU must be informed in writing.

The PI or delegate must make every effort to ensure that the specific wishes of any participant who wishes to withdraw consent for further involvement in the study are defined and documented using the Withdrawal CRF in order that the correct processes are followed by the CTRU and research site following the withdrawal of consent.

9.9 Definition of End of Study

The end of the study is defined as the date that the last participant has their last follow-up assessment.

10 Safety Reporting

For the purpose of the SaFaRI study, which involves surgical interventions, the safety reporting terms adverse events and serious adverse events have been translated into complications.

10.1 General Definitions

A **complication** is defined as an untoward medical event in a participant, which has a causal relationship to the study. The study includes the surgical intervention and any study-specific interventions e.g. the consent process and completion of questionnaires.

An untoward medical event can include:

- any unintentional, unfavourable clinical sign or symptom
- any new illness or disease or the deterioration of existing condition
- any clinically relevant deterioration in any clinical tests

A **serious complication** is defined as a complication which:

- results in death
- is life-threatening[6]
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect, or
- is otherwise considered medically significant by the investigator

A **serious** complication which is **related** and **unexpected** (termed **Unexpected Serious Complication**, or **USC**) will require expedited reporting (see section 10.3.1) to enable reporting to the main Research Ethics Committee (REC) and Sponsor.

The National Research Ethics Service (NRES) defines the terms **related** and **unexpected** as:

- **Related**: that is, it resulted from administration of any research procedures. All complications by definition are related to the study procedures. (Untoward medical events which are unrelated to the study procedures are not being collected in this study.)
- **Unexpected**: that is, the type of event that in the opinion of the investigator is not considered expected. Examples of expected complications are provided in section 10.2; note this is not an exhaustive list.

10.2 SaFaRI Expected Complications

10.2.1 General Operative Expected Complications

- Cardiorespiratory complication
- Urinary retention
- Nerve dyspraxia

[6] Life-threatening refers to an event in which the participant was at risk of death at the time of the event, NOT an event which hypothetically may have caused death had it been more severe.

- Complications relating to spinal/local anaesthetic (anaesthetic toxicity, spinal headache, lumbar/leg pain, haematoma, infection)
- Deep vein thrombosis
- Wound haematoma
- Wound infection
- Faecal contamination
- Haemorrhage (more than anticipated)
- Failure of surgical equipment (device malfunction, necessary instruments/device not available)
- Radiological imaging not available

10.2.2 SNS Device-related Expected Complications

- Failed implant procedure
- Post-operative bleeding
- Wound infection
- Implant infection
- Electrode dislodgement (temporary SNS)
- Lead migration/fragmentation (permanent SNS)
- Neurological pains in legs, perineum, vagina
- Pain at battery site (permanent SNS) due to non-infective cause, e.g. battery rotation
- Lack or loss of efficacy

10.2.3 FENIX$_{TM}$ MSA Device-related Expected Complications

- Failure to implant (e.g. wound contamination, rectal/vaginal injury)
- Peri-operative bleeding/haematoma
- Transient anal/rectal pain
- Wound infection
- Implant infection
- Device failure/separation
- Device migration
- Device erosion
- Device explant/reoperation
- Worsening constipation/obstructed defaecation

10.3 Reporting of Complications

Information on all complications will be collected for this study whether volunteered by the participant, discovered by investigator questioning or detected through physical examination or other investigation.

10.3.1 Serious Complication (SCs) and Unexpected Serious Complications (USCs) occurring within 30 days of surgery – Expedited reporting

All Serious Complications (SCs) and Unexpected Serious Complications (USCs) (see section 10.1) occurring up to 30 days following surgery are subject to expedited reporting requirements and must therefore be notified to the CTRU **within 24 hours** of the clinical research staff becoming aware of the event. Notifications must be sent to CTRU by fax using the SC / USC CRF.

24 hr fax for reporting SC & USCs: 0113 343 6774

For each SC and USC, the following data will be collected:

- Start and end dates of event, if resolved
- Full details of complication in medical terms with a diagnosis (if possible)
- Action/intervention
- Outcome
- An identifiable and authorised reporting source (i.e. the signature of the investigator or other medic authorised by the investigator at the reporting research site)

Any follow-up information on SCs and USCs must be faxed to the CTRU as soon as it is available. Events will be followed up until the event has resolved or a final outcome has been reached. All SCs and USCs will be reviewed by the Chief Investigator (CI). USCs will be subject to expedited reporting to the Sponsor and the REC by the CTRU on behalf of the CI in accordance with current NRES guidance, CTRU Standard Operating Procedures (SOPs), and Sponsor requirements. USCs and SCs relating to the FENIX$_{TM}$ MSA device will be reported onto Torax® Medical, Inc.

SCs and USCs with an onset date greater than 30 days post-surgery are not subject to expedited reporting, but must be reported with all other types of complication (i.e. non-serious expected and unexpected complications) via a post-operative complication form submitted with the 6, 12 & 18-months Post-randomisation Follow Up Assessment CRFs, as appropriate (see section 10.3.2).

10.3.2 All other complications – Non-expedited reporting

Information about the incidence and severity of all other complications (this includes all non-serious expected and unexpected complications) which occur from the date of operation until 18 months post-randomisation will be collected for all participants on the operative CRF, post-operative review CRF, 6, 12 or 18 -month post-randomisation CRFs , as appropriate. This also applies to any SCs or USCs with an onset date greater than 30 days post surgery.

These events will **not** be subject to expedited reporting requirements.

10.3.3 Untoward medical events unrelated to the study – Not reportable

It is anticipated that there will be minimal additional risks associated with the interventions in this study. Participants treated may have co-morbidities and in recognition of this, untoward medical events will only be reported if they are classified as related to study procedures (including the surgical intervention and related procedures or study-specific procedures such as consent and questionnaire completion).

10.4 Responsibilities for Safety Reporting

Principal Investigator (PI) (i.e. lead study clinician at each recruiting research site or appropriate clinical individual identified in the APL)

- Checking for complications during admission and follow-up, including judgment in assigning:
    - Causality, i.e. whether an untoward medical event is related (i.e. a complication which therefore needs to be reported) or unrelated (i.e. not a complication and therefore does not need to be reported)
    - Seriousness
    - Expectedness
- To ensure all SCs and USCs up to 30 days post-operation are recorded and initially reported to the CTRU within 24 hours of the research site team becoming aware and to provide further follow-up information as soon as available.
- To report SCs and USCs to the CTRU in-line with the protocol.

Chief Investigator (CI) (or nominated individual in CI's absence)

- Assign relatedness and expected nature of reported complications/untoward medical events where it has not been possible to obtain local assessment.
- Undertake review of SCs and USCs (see section 10.1).
    - In the event of disagreement between local assessment and the CI, local assessment may be upgraded or downgraded by the CI prior to reporting to the REC.

Clinical Trials Research Unit (CTRU)

- Expedited reporting of USCs occurring within 30 days post-operation to the REC and Sponsor within required timelines.
- Expedited reporting of SCs and USCs relating to the FENIX$_{TM}$ MSA device to Torax® Medical, Inc.
- Preparing annual safety reports to the REC and periodic safety reports to the Trial Steering Committee (TSC) and Data Monitoring & Ethics Committee (DMEC) as appropriate.
- Notifying Investigators of SCs and USCs which compromise participant safety.

Trial Steering Committee (TSC)

- Periodic review of safety data in accordance with the TSC Terms of Reference, and liaising with the DMEC regarding safety issues.

Data Monitoring & Ethics Committee (DMEC)

- In accordance with the DMEC Terms of Reference, periodic review of unblinded safety data to determine patterns and trends of events and to identify any safety issues which would not be apparent on an individual case basis.

10.5 Reporting

Safety issues will be reported to the REC in the annual progress report.

An annual summary of complications will be reported to the TSC and Sponsor.

Expedited reporting of events (as detailed in section 10.3.1) to the REC, Torax® Medical, Inc. and Sponsor will be subject to current NRES guidance, CTRU SOPs and Torax® Medical, Inc. and Sponsor requirements.

11 Participant Questionnaires

Participants will complete a number of questionnaires designed to capture FI symptoms, constipation symptoms, QoL and the costs involved with each treatment.

- Cleveland Clinic Incontinence Score (CCIS): assesses five parameters associated with incontinence: incontinence to solid, liquid, and gas, use of pads, and lifestyle restriction. Each parameter is scored 0-4, with “0” for never and “4” for every day. The five parameters are added to give a total score out of 20.
- Obstructed Defecation Score (OD-score): consists of 5 items: excessive straining, incomplete rectal evacuation, use of enemas and/or laxatives, vaginal-anal-perineal digitations, and abdominal discomfort and/or pain. Each item is graded from 0 to 4 with a score ranging from 0 (no symptoms) to 20 (very severe symptoms).

- Faecal Incontinence Quality of Life Questionnaire (FIQoL): is composed of 29 items that make up 4 scales: Lifestyle (10 items), Coping/Behaviour (9 items), Depression/Self-Perception (7 items), and Embarrassment (3 items). Scoring is derived from a participant completed questionnaire that assesses the impact of FI on 4 domains of QoL. Scales range from 1 to 5, with 1 indicating a lower functional QoL. Scale scores are derived by averaging the response to all items in the scale.
- Health and social care resource use: is composed of questions related to contact with primary, community and social care services. The questionnaire consists primarily of 'tick-box' completion questions.
- SF-12®: is a 12-item subset of the SF-36v2® that measures the same eight domains of health. It is a brief, reliable measure of overall health status. It is useful in large population health surveys and has been used extensively as a screening tool.
- EQ-5D-5L$_{TM}$: a well-validated questionnaire used to assess generic QoL, provides a simple descriptive profile and a single index value for health status.

Participants will complete all questionnaires at baseline[7] and at 6, 12 and 18 months post-randomisation. Baseline questionnaires will be completed at clinic and participants will be asked to seal the questionnaires in envelopes prior to being given to research staff. Research staff will then send the sealed envelopes to the CTRU for entry into the database. Participant questionnaires at 6, 12 and 18 months post-randomisation will be received by the participants via post (these will be posted from the CTRU) who complete them at home and return them to the CTRU using a pre-supplied stamped addressed envelope. A thank you letter will be sent to participants by CTRU upon receipt of a completed questionnaire. Should a completed questionnaire not be received at CTRU by the required timepoint, CTRU will send a reminder letter to the participant.

In addition to these time-points, participants will complete the CCIS and the Health and social care resource use questionnaire 2 weeks post-operatively (only for temporary SNS, and FENIX$_{TM}$ MSA). For the permanent SNS, participants will complete the Health and social care resource use questionnaire 2 weeks post-operatively. These will be completed at clinic and participants will be asked to return them to the CTRU by handing them to research staff.

The timings of completion of participant-completed questionnaires are summarised in Table 2. All participants will be followed up as per protocol until 18 months post-randomisation.

[7] Baseline questionnaires must be completed after consent and, wherever possible, prior to randomisation (where this is not possible, they must be completed prior to the participant being made aware of their randomised operation (SNS or FENIX$_{TM}$ MSA).

Table 2: Schedule of Events for Participant Questionnaires

	Baseline[1]	Post-operative Review[1] (temp SNS & FENIX$_{TM}$ MSA)	Post-operative Review[1] (permanent SNS)	6[2], 12 and 18 months Post-randomisation Assessment
CCIS	√	√		√
OD-score	√			√
FIQoL	√			√
EQ-5D$_{TM}$	√			√
SF-12®	√			√
Health and Social Care Resource use	√	√	√	√

[1] Participant questionnaires completed at clinic.

[2] Participant questionnaires posted out to the participants by CTRU.

12 Economic Evaluation

The objective of the economic evaluation is to identify the within study and long-term incremental cost-effectiveness ratios for FENIX$_{TM}$ MSA vs. SNS for adult FI.

12.1 Measurement of Outcomes

The within study economic evaluation will use QALYs outcome measures. The estimation of QALYs requires the production of utility weights for each health state observed in the study population. We will use the EQ-5D$_{TM}$ (EuroQol) instrument for this purpose. [xx] The EQ-5D$_{TM}$ is a very simple instrument to complete and will therefore be collected at baseline and by post at 6, 12 and 18 months post randomisation. This will limit the need to interpolate quality of life between observation points and the associated inaccuracy in the estimation of the Health Related Quality of Life (HRQoL) differences between therapies. [xxi] However, whilst the EQ-5D$_{TM}$ is the NICE preferred measure of HRQoL its sensitivity to detect changes in FI is unproven; we have therefore included the SF-12® as the source of utility data, and will undertake a secondary analysis using the SF-12® to derive utility values [xxii] and present this alongside the EQ-5D$_{TM}$ data. [xxiii]

12.2 Measurement of Resources Use

NHS resource use associated with each treatment modality will be collected either through the CRF (investigations, drugs, referrals for other services), Hospital Episode Statistics (HES) data (in-patient, out-patient and Accident & Emergency) or through a participant questionnaire (contact with primary, community and social care services). The participant questionnaire will be designed to allow tick-box completion where ever possible. Whilst participants are attending clinic at baseline they will receive and return their participant questionnaire at the outpatient clinic. For the remaining time periods, they will receive the participant questionnaire by post and will return it to the study site using a freepost envelope.

12.3 Identifying Unit Costs

Unit costs for health service resources will be obtained from national sources such as the Personal Social Services Research Unit (PSSRU), the British National Formulary (BNF) and NHS Reference cost database. Where national unit costs are not available the finance departments of NHS Trusts participating in the study will be asked to provide local cost data. The mean of these costs will be used as the unit cost estimate in the analysis.

12.4 Analysis

The cost effectiveness analysis will adopt the perspective of the NHS and social services.

There remains some uncertainty regarding the correct approach to discounting costs and benefits. The analysis will follow the recommendations current at the time. Under current recommendations this would mean that costs and outcomes would be discounted at 3.5% per annum. [xxiv]

The non-parametric bootstrap method will be used to produce a within-study probabilistic sensitivity analysis of the incremental cost effectiveness ratio. In addition to presenting the expected incremental cost effectiveness ratio, we will present the scatterplot on the cost effectiveness plane, the 95% cost effectiveness ellipse and the cost effectiveness acceptability curve. [xxv]

12.5 Modelling the long-term cost effectiveness

The exact structure and duration of the long term cost effectiveness model will be established in discussions with the clinicians on the study team and after analysis of the complication data observed in the study. It is likely that the model will be a Markov or semi-Markov state model. As far as possible, the transition rates for the model will be estimated from the clinical study data. For model parameters for which data could not be collected within the study; e.g. long-term outcomes, we will follow recommended best practice in identifying and synthesising the best available evidence in the literature. The long-term cost effectiveness modelling will adopt the strategies for addressing issues of perspective and discounting as the within study analysis. We will in addition undertake an expected value of information analysis.

13 Endpoints

13.1 Primary Endpoint

The primary endpoint is success, as defined by device in use and ≥50% improvement[8] in the participant-reported CCIS, at 18-months post-randomisation.

13.2 Secondary Endpoints

Secondary end-points include:

- Safety of FENIX$_{TM}$ MSA or SNS, as judged by explant rates, operative[9] and post-operative[10] complications
- Change from baseline in generic and disease-specific quality of life as measured by CCIS, OD-score, FiQOL, EQ-5D$_{TM}$ and SF12® at 6, 12 and 18 months post-randomisation
- Cost-effectiveness
- Success at 6 and 12 months as defined in the primary endpoint

[8] Between the baseline and 18-month scores.

[9] This includes those occurring during theatre-time and post-surgery hospital stay.

[10] Up to and including 12 months from the date of the last study surgery.

14 Statistical Considerations

14.1 Sample size

350 participants will be required to detect at least a 20% difference in the percentage of successes at 18-months post-randomisation (where success is defined to be: device in use and ≥50% CCIS improvement from baseline) between FENIX$_{TM}$ MSA and SNS at 5% level of significance, 90% power, assuming approximately 40% success on the SNS arm and allowing for 20% loss to follow-up.

A sample size of 350 participants is also expected to sufficiently guard against the potential adverse effects of clustering by surgeon on the study power. Assuming that the number of participants recruited per surgeon is no larger than 15 (i.e. recruitment of at least 24 surgeons to the study), a sample size of 350 participants will yield at least 80% power for intra-cluster correlation coefficients (ICCs) as large as 0.025.

15 Statistical Analysis

Statistical analysis is the responsibility of the CTRU Statistician. A full statistical analysis plan will be written before any analyses are undertaken and in accordance with CTRU standard operating procedures.

Analysis will be performed on an intention-to-treat (ITT) basis (primary analysis), where participants will be included according to the surgical procedure they were randomised to, and by actual treatment group, where participants will be included according to the surgery actually received (SNS device or FENIX$_{TM}$ MSA device implantation). All hypothesis tests will be two-sided and use a 5% significance level.

Analyses will exclude training cases, although data collected on training cases will be summarised.

Analysis and reporting will be in line with CONSORT (Consolidated Standards of Reporting Trials) guidelines. For the primary analysis multi-level logistic regression will be used, including adjustment for the factors included in the minimisation algorithm.

Secondary endpoints including SF-12®, EQ-5D$_{TM}$, CCIS and OD-score recorded at baseline, 6, 12 and 18 months post-randomisation will be analysed using random effects (multi-level) models to account for the hierarchical nature of repeated measures data. The models will include adjustments for minimisation factors, and a categorical covariate will be used to assess the effect of length of time of device in use on these endpoints.

Pattern-mixture multi-level models, which will treat all participant data observed after the removal of their device (explant) as missing data, but also account for the informative nature of the missing data, will be fitted to the secondary endpoints outlined above. Note that this is in contrast to the random effects models outlined above, which incorporate data from participants ‘post-explant’. Therefore the results yielded by the pattern-mixture multi-level models will act as sensitivity analyses which can be used to explore the potential issue of disparity in treatment of participants post-explant in each treatment arm.

A subgroup analysis will be performed on participants in the FENIX$_{TM}$ arm in order to explore which potential patients could benefit most from FENIX$_{TM}$. A multi-level logistic regression model will be fitted using the primary endpoint and the effects of various patient-level covariates (e.g. age, gender, baseline QoL) on the odds of 'success' will be assessed.

Data collected on the safety of FENIX$_{TM}$ MSA and SNS will be analysed using multi-level logistic regression.

A DMEC will be set up to independently review data on safety and recruitment. Interim reports will be presented to the DMEC in strict confidence, in at least yearly intervals. This committee, in light of the interim data, and of any advice or evidence they wish to request, will advise the TSC if there is proof beyond reasonable doubt that one treatment is better. No formal interim analyses are planned hence no statistical testing will take place until final analysis.

16 Data Monitoring

Study supervision will be established according to the principles of GCP and in-line with the NHS Research Governance Framework (RGF). This will include establishment of a core Project Team, Trial Management Group (TMG), an independent TSC and independent DMEC.

16.1 Data Monitoring and Ethics Committee

An independent DMEC will be appointed to review the safety and ethics of the study, alongside study progress and the overall direction as overseen by the TSC. Detailed un-blinded reports will be prepared by the CTRU for the DMEC at approximately yearly intervals.

The DMEC will be provided with detailed un-blinded reports containing the following information:

- Rates of occurrence of unexpected serious complications (USCs; see section 10.1) by treatment group
- Time between randomisation and surgery by treatment group for each participating research site
- Rates of intra-operative and post-operative complications by treatment group for each participating surgeon

Study progress will be closely monitored by the independent DMEC, who will report to the TSC, and the overall direction overseen by the TSC (ensuring regular reports to the NIHR Health Technologies Assessment (HTA) programme).

16.2 Data Monitoring

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until they are received, until confirmed as not available, or until the study is at analysis.

The CTRU or study Sponsor will reserve the right to intermittently conduct source data verification (SDV) exercises on a sample of participants, which will be carried out by staff from the CTRU or study Sponsor. SDV will involve direct access to participant medical notes at the participating research sites and the ongoing central collection of copies of consent forms and other relevant investigation reports.

A Study Monitoring Plan will be developed.

16.3 Clinical Governance Issues

To ensure responsibility and accountability for the overall quality of care received by participants during the study period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the TSC and, where applicable, to individual research sites.

17 Quality Assurance, Ethical Considerations, and Confidentiality

17.1 Quality Assurance

The study will be conducted in accordance with the principles of GCP in clinical trials, the NHS RGF and through adherence to CTRU SOPs.

The CTRU and Sponsor have systems in place to ensure that serious breaches of GCP or the study protocol are picked up and reported. Investigators are required to **immediately** notify the CTRU of a serious breach (as defined in the latest version of the NRES SOP) that they become aware of. A 'serious breach' is defined as a breach of the protocol or of the conditions or principles of GCP (or equivalent standards for conduct of non-CTIMPs) which is likely to affect to a significant degree the safety or physical or mental integrity of the study subjects, or the scientific value of the research.

In the event of doubt or for further information, the Investigator should contact the Senior Trial Co-ordinator at the CTRU.

17.2 Ethical Considerations

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013. Informed written consent will be obtained from the participants prior to randomisation into the study. The right of a patient to refuse participation

without giving reasons must be respected. The participant must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment.

17.2.1 Ethical approval

Ethical approval will be sought through NRES. The study will be submitted to and approved by a REC and the appropriate Site Specific Assessor for each participating research site prior to entering participants into the study. The CTRU will provide the REC with a copy of the final protocol, participant information sheets, consent forms and all other relevant study documentation.

17.3 Confidentiality

All information collected during the course of the study will be kept strictly confidential. Information will be held securely on paper at the CTRU. In addition, the CTRU will hold electronic information on all study participants. The CTRU will have access to the entire database for monitoring, co-ordinating, and analysis purposes.

The CTRU will comply with all aspects of the 1998 Data Protection Act. Operationally this will include:

- Explicit written consent from participants to record personal details including name, date of birth, NHS number.
- Appropriate storage, restricted access and disposal arrangements for participants' personal and clinical details.
- Consent from participants for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to study participation.
- Consent from participants for the data collected for the study to be used to evaluate safety and develop new research.
- Copies of participants consent forms, which will include participants names, will be collected when a participants is randomised into the study by the CTRU. All other data collection forms that are transferred to or from the CTRU will be coded with a unique participant study number and will include two participant identifiers, usually the participant's initials and date of birth.
- Where central monitoring of source documents by CTRU (or copies of source documents) is required (such as scans or local blood results), the participant's name must be obliterated by site before sending.
- Where anonymisation of documentation is required, research sites are responsible for ensuring only the instructed identifiers are present before sending to CTRU.

If a participant withdraws consent from further study treatment and/or further collection of data, their data will remain on file and will be included in the final study analysis.

17.4 Archiving

17.4.1 Study data and documents held by CTRU

At the end of the study, all data held by the CTRU and all study data will then be securely archived in line with the Sponsor's procedures for a minimum of 10 years.

17.4.2 Study data and documents held by research sites

Research sites are responsible for archiving all study data and documents (ISF and all essential documents therein, including CRFs) at the participating research site until authorisation is issued from the Sponsor for confidential destruction.

17.4.3 Participant medical records held by research sites

Research sites are responsible for archiving study participant medical records in accordance with the site's policy and procedures for archiving medical records of patients who have participated in a clinical study. However, participant medical records must be retained until authorisation is received from the Sponsor for confidential destruction of study documentation.

18 Statement of Indemnity

The University of Leeds will be liable for negligent harm caused to participants treated in the UK that is caused by the design of the study.

The NHS has a duty of care to patients treated in the UK, whether or not the patient is taking part in a clinical study, and the NHS remains liable for harm to UK patients due to clinical negligence under this duty of care.

19 Study Organisational Structure

Research sites will liaise with the CTRU for advice and support on study set-up and operation, and submission of study data. In turn, the CTRU will be responsible for data chasing.

19.1 Responsibilities

The CI is responsible for the design, management and reporting of the study.

The CTRU will have responsibility for overall conduct of the study in accordance with the NHS RGF and CTRU SOPs.

The responsibility for ensuring clinical management of participants is conducted in accordance with the study protocol ultimately remains with the PI at each research site.

19.2 Operational Structure

Chief Investigator (CI): the CI is involved in the design, conduct, co-ordination and management of the study.

Trial Management Group (TMG): the TMG, comprising the CI, CTRU team, other key external members of staff involved in the study, and a patient representative will be assigned responsibility for the clinical set-up, on-going management, promotion of the study, and for the interpretation of results. Specifically the TMG will be responsible for:

- Protocol completion
- CRF development
- Obtaining approval from the REC and supporting applications for Site Specific Assessments (SSAs)
- Completing cost estimates and project initiation
- Nominating members and facilitating the TSC and DMEC
- Reporting of complications
- Monitoring of screening, recruitment, treatment and follow-up procedures
- Auditing consent procedures, data collection, study end-point validation and database development.

Clinical Trials Research Unit (CTRU): the CTRU will provide set-up and monitoring of study conduct to CTRU SOPs including randomisation design and service, database development and provision, protocol development, CRF design, study design, source data verification, ongoing management including training, monitoring reports and study promotion, monitoring schedule and statistical analysis for the study. In addition, the CTRU will support ethical approval submissions, any other site-specific approvals, and clinical set-up. The CTRU will be responsible for the overall day-to-day running of the study including study administration, database administrative functions, data management, safety reporting, and all statistical analyses.

Trial Steering Committee (TSC): the TSC will provide overall supervision of the study, in particular study progress, adherence to protocol, participant safety and consideration of new information. It will include an Independent Chair, not less than two other independent members, and a consumer representative. The CI and other members of the TMG may attend the TSC meetings and present and report progress. The Committee will meet annually as a minimum.

Data Monitoring and Ethics Committee (DMEC): the DMEC will review the safety and ethics of the study by reviewing interim data during recruitment and follow-up. The Committee will meet annually as a minimum.

Torax® Medical, Inc.: are manufacturers of the FENIX$_{TM}$ MSA device and will be providing devices for study use at a discounted cost. Torax® Medical, Inc. will also provide support and proctorship for surgeons at the initial study implantation operations.

Bladder & Bowel Foundation (B&BF): will facilitate the promotion of the study and dissemination of outputs and will provide review of study documentation through their network of contacts (patient and public representatives and their membership of the wider population of incontinence sufferers).

19.3 Funding

The research grant for this study has been awarded by the HTA programme which is managed by the NIHR.

20 Publication Policy

The study will be registered with an authorised registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines prior to the start of recruitment.

The success of the study depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the study, through authorship and contributorship. Authorship decisions will be guided by standard requirements for authorship relating to submission of manuscripts to medical journals. These state that authorship credit should be based only on the following conditions being met (http://www.icmje.org):

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data
- Substantial contribution to drafting the article or revising it critically for important intellectual content
- Substantial contribution to final approval of the version to be published.

In light of this, the CI, other SaFaRI grant applicants, and relevant senior CTRU staff will be named as authors in any publication, subject to journal authorship restrictions. In addition, all collaborators (surgeons) will be listed as contributors for the main study publication, giving details of roles in planning, conducting and reporting the study. It is planned that the top five recruiting surgeons will also be named as authors dependent on publication restrictions.

To maintain the scientific integrity of the study, data will not be released prior to the first publication of the analysis of the primary endpoint, either for study publication or oral presentation purposes, without the permission of the TSC. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the study until the first publication of the analysis of the primary endpoint. Publications relating to methodological issues in SaFaRI may be published prior to publication of the primary endpoint analysis.

On completion of the research project a draft final report will be submitted to the HTA programme (study funder) by the CTRU, within 14 days. This will be peer reviewed and then published on the HTA website. The CTRU is obliged to provide NIHR/HTA with advanced notice of any publication relating to the study. Copies of any materials intended for publication will be provided to NIHR/HTA at least 28 days prior to submission for publication.

21 Abbreviations Used

ACRONYM	DEFINITION
ABS	Artificial Bowel Sphincter
ACPGB&I	Association of Coloproctology of Great Britain and Ireland
APL	Authorised Personnel Log
ASA	American Society of Anesthesiologists
BNF	British National Formulary
CCIS	Cleveland Clinic Incontinence Score
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring & Ethics Committee
FI	Faecal Incontinence
FIQoL	Faecal Incontinence Quality of Life
GCP	Good Clinical Practice
HE	Health Economics
HRQoL	Health Related Quality of Life
HES	Hospital Episode Statsitics
ICC	Intra-cluster Correlation Coefficient
ICER	Incremental Cost-Effectiveness Ratio
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
ISF	Investigator Site File
ITT	Intention To Treat
MCA	Mental Capacity Act 2005
MRI	Magnetic Resonance Imaging
MRU	Medical Resource Utilisation
MSA	Magnetic Sphincter Augmentation
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NIHR HSC	NIHR Horizon Scanning Centre
NIHR HTA	NIHR Health Technologies Assessment

NRES	National Research Ethics Service
OD-score	Obstructed Defecation score
PI	Principal Investigator
PIN	Personnel Identification Number
PIS	Participant Information Sheet
PNE	Percutaneous Nerve Evaluation
PSSRU	Personal Social Services Research Unit
QALY	Quality Adjusted Life Year
QoL	Quality of Life
REC	Research Ethics Committee
RGF	Research Governance Framework
SC	Serious Complication
SDV	Source Data Verification
SNS	Sacral Nerve Stimulation
SOP	Standard operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
US	United States
USC	Unexpected Serious Complication

22 References

[i] Maeda Y, Lundby L, Buntzen S, Laurberg S. Suboptimal outcome following sacral nerve stimulation for faecal incontinence. BJS 2011; 98: 140-7.

[ii] Ferrara A, De Jesus S, Gallagher JT, Williamson PR, Larach SW, Pappas D, Mills J, Sepulveda JA. Time-related decay of the benefits of biofeedback therapy. Techniques in Coloproctology. 2001; 5: 131-5.

[iii] Maeda Y. Laurberg S. Norton C. Perianal injectable bulking agents as treatment for faecal incontinence in adults. Cochrane Database of Systematic Reviews. (5):CD007959, 2010.

[iv] See endnote i above.

[v] Mundy L, Merlin TL, Maddern GJ, Hiller JE. Systematic review of safety and effectiveness of an artificial bowel sphincter for faecal incontinence. Br J Surg. 2004; 91: 665– 672.

[vi] Chapman AE, Geerdes B, Hewett P, Young J, Eyers T, Kiroff G et al. Systematic review of dynamic graciloplasty in the treatment o faecal incontinence. Br J Surg. 2002; 89: 138-53. NICE Interventional Procedure Guidance 159. Stimulated gracioloplasty for faecal incontinence. March 2006.

[vii] Matzel KE, Stadelmaier U, Hohenfellner M, Gall FP. Electrical stimulation of sacral spinal nerves for treatment of faecal incontinence. Lancet 1995; 346: 1124-7.

[viii] See endnote i above. Elenhorst J, Koch SM, Uludag O, van Gemert WG, Baeten CG. Sacral neuromodulation in patients with faecal incontinence: results of the first 100 permanent implantations. Colorectal Dis. 2007; 9: 725-30. Tjandra JUJ, Lim JF, Matzel K. Sacral nerve stimulation: an emerging treatment for faecal incontinence. ANZ Journal of Surgery 2004; 74: 1098-106. Altomare DF, Ratto C, Ganio E, Lolli P, Main A, Villani RD. Long-term outcome of sacral nerve stimulation for fecal incontinence. Dis Colon Rect 2009; 52: 11-7.

[ix] Dudding TC, Meng Lee E, Faiz O, Pares D, Vaizey CJ, McGuire A, Kamm MA. Economic evaluations of sacral nerve stimulation or faecal incontinence. Br J Surg. 2008; 95:1153-63.

[x] Hetzer FH, Bieler A, Hahnloser D, Lohlein F, Clavien PA, Demartines N. Outcome and cost analysis of sacral nerve stimulation for faecal incontinence. Br J Surg. 2006; 93: 1411-17.

[xi] NICE: Interventional Procedure Guidance 99: sacral nerve stimulation for faecal incontinence. Nov 2004. http://www.nice.org.uk/nicemedia/live/11079/30919/30919.pdf

[xii] Matzel KE. Sacral nerve stimulation for faecal incontinence: its role in the treatment algorithm. Colorectal Dis. 2011; 13: 10 – 14.

[xiii] Elenhorst J, Koch SM, Uludag O, van Gemert WG, Baeten CG. Sacral neuromodulation in patients with faecal incontinence: results of the first 100 permanent implantations. Colorectal Dis. 2007; 9: 725-30. Tjandra JUJ, Lim JF, Matzel K. Sacral nerve stimulation: an emerging treatment for faecal incontinence. ANZ Journal of Surgery 2004; 74: 1098-106. Hetzer FH, Hanhloser D, Clavien PA, Demartines X. Quality of life and morbidity after permanent sacral nerve stimulation for fecal incontinence. Arch Surg 2007; 142: 8-13.

[xiv] Barussaud, M-L, Mantoo S., Wyart V., Meurette G., and Lehur, P.-A. The magnetic anal sphincter in faecal incontinence: is initial success sustained over time? Colorectal Dis. 2013: 15: 1499-1503.

[xv] Wong MTC, Meurette G, Stanherlin P, Lehur PA. The magnetic anal sphincter versus the artificial bowel sphincter: a comparison of 2 treatments for fecal incontinence. Dis Colon Rectum 2011; 54: 773-9.

[xvi] Hetzer FH, Bieler A, Hahnloser D, Lohlein F, Clavien PA, Demartines N. Outcome and cost analysis of sacral nerve stimulation for faecal incontinence. Br J Surg. 2006; 93: 1411-17.

[xvii] Gray M. How to get better value health care. Whitney.Oxford: The Alden Press, 2007.

[xviii] http://www.hsc.nihr.ac.uk/topics/fenix-continence-restoration-system-for-severe-chr/

[xix] National Institute for Health and Clinical Excellence. The management of faecal incontinence in adults. Clinical Guideline CG49. London: NICE; June 2007.

[xx] Brooks RG, et al. EuroQoL: health-related quality of life measurement. Results of the Swedish questionnaire exercise. Health Policy 1991; 18: 37-48. Kind P, Dolan P. The effect of past and present illness experience on the valuations of health states. Med Care. 1995 ; 33(4 Suppl) : AS255-63.

[xxi] Manca A, Hawkins N, Sculpher MJ, Estimating Mean QALYs in Trial-based Cost-effectiveness Analysis: The Importance of Controlling for Baseline Utility, Health Economics 2006, 14(5), 487-96.

[xxii] Brazier J.E., Roberts J, Deverill M. The estimation of a preference based measure of health from the SF-36. Journal of Health Economics. 2002; 21: 271- 292.

[xxiii] National Institute of Health and Clinical Excellence. 2008. Guide to the methods of technology appraisal. London.

[xxiv] See endnote xxiii above. Brouwer WB, Niessen LW, Postma MJ, and Rutten FF. Need for differential discounting of costs and health effects in cost effectiveness analyses. BMJ 2005; 331(7514):446-8. Claxton K, Sculpher M, Culyer A, McCabe C, et al. Discounting and cost-effectiveness in NICE – stepping back to sort out a confusion. Health Econ. 2006 ;15(1):1-4.

[xxv] Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart G. Textbook: Methods for the Economic Evaluation of Health Care Programmes (Third Edition), Oxford University Press, June 2005.