Sacral nerve stimulation versus the magnetic sphincter augmentation device for adult faecal incontinence: the SaFaRI RCT

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Declared competing interests of authors: David G Jayne reports grants from National Institute for Health Research (NIHR) Senior Investigator awards, and that he was a member of the NIHR Efficacy and Mechanism Evaluation (EME) Strategy Group and Prioritisation Group (2015–18) and NIHR Clinical Scientist Awards Panel (2015–2018). He currently sits on the NIHR Advanced Fellowship Panel (2018 to present) and is a member of the NIHR i4i Product Development Awards Committee (2019 to present). Julia M Brown reports grants from NIHR Senior Investigator awards and the NIHR Funding Committee during the conduct of the study, and declares membership of the Health Technology Assessment (HTA) Remit and Competitiveness Group (2016 to present), Clinical Trial Units funded by NIHR, the HTA Funding Committee Policy Group (2016 to present) and the HTA Clinical Evaluation and Trials Committee (2016 to present). Claire Hulme was a member of the NIHR HTA Commissioning Board (2013–17). Steven Brown was a member of the HTA Commissioning Board (2018–19). David Meads was a member of the NIHR HTA Elective and Emergency Specialist Care (EESC) Methods Group (2014–17) and NIHR HTA EESC Panel (2013–17). He is a member of a NIHR Programme Grants for Applied Research subpanel (2017 to present).

Published March 2021
DOI: 10.3310/hta25180

Scientific summary

The SaFaRI RCT

Health Technology Assessment 2021; Vol. 25: No. 18
DOI: 10.3310/hta25180

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Faecal incontinence is a distressing condition that affects between 5% and 10% of the adult population. Current treatment options include conservative measures with dietary modification and constipating agents, pelvic floor physiotherapy with or without biofeedback therapy, and surgical intervention for patients with moderate to severe symptoms. The most commonly used surgical intervention for patients with faecal incontinence resistant to medical treatment is sacral nerve stimulation. Sacral nerve stimulation involves a two-stage procedure, whereby a temporary stimulation phase is used to assess initial efficacy and if a $\geq$ 50% reduction in weekly incontinence episodes or incontinence score is observed, then the patient may proceed to a permanent sacral nerve stimulation implant. Sacral nerve stimulation is recommended by the National Institute for Health and Care Excellence and, although short-term efficacy is reported to be good, the long-term efficacy as reported from a decision-to-treat perspective is only around 45–50%. Despite the high costs of the permanent implant, sacral nerve stimulation is believed to be cost-effective compared with the only other definitive treatment for faecal incontinence: a permanent colostomy.

More recently, a new device, FENIX™ (Torax Medical, Minneapolis, MN, USA), has been introduced to the market, consisting of a string of magnetic beads that is implanted around the anal canal to augment the anal sphincter. Initial results from small, single-centre studies have been promising, suggesting a $\geq$ 50% improvement in incontinence in around 70% of participants, with a complication rate of 20% and a device explant rate of 10%. Only one previous randomised trial has been undertaken to evaluate the FENIX device, comparing it with the Acticon Neosphincter® (American Medical Systems, Minneapolis, MN, USA) and showing benefits in terms of shorter operating times and length of hospitalisation, and reduced costs.

Objectives

The objective was to undertake a randomised comparison of the safety, efficacy, and cost-effectiveness of the FENIX device with sacral nerve stimulation for the treatment of adults with moderate to severe faecal incontinence that is resistant to medical therapies. The primary outcome was success of the intervention (FENIX or sacral nerve stimulation) defined as the device in use and $\geq$ 50% improvement in the participant-reported Cleveland Clinic Incontinence Score at 18 months post randomisation. The secondary outcomes included length of hospital stay, complications, reinterventions, constipation, quality of life and cost-effectiveness.

Methods

A multicentre randomised controlled trial was undertaken across 18 NHS hospital trusts involving colorectal surgeons who were members of the Association of Coloproctology of Great Britain and Ireland. It was estimated that 350 participants would be required to detect at least a 20% difference in the percentage of successes at 18 months post randomisation, where success was defined as the device in use and $\geq$ 50% improvement in Cleveland Clinic Incontinence Score from baseline. Prior to randomising participants, all surgeons had to have performed a minimum of 10 permanent sacral nerve stimulation implants, observed a minimum of one FENIX procedure and performed two FENIX procedures under proctorship with data captured in the registration phase of the study. For inclusion in the study, participants had to be aged $\geq$ 18 years and to have been suffering from faecal incontinence

for more than 6 months with ≥ 2 incontinent episodes per week. The aetiology of incontinence was not specified and an anal sphincter defect of ≤ 180°, as assessed by endoanal ultrasound scan, was allowed. Participants were randomised equally to either FENIX or sacral nerve stimulation treatment, with minimisation factors including the treating surgeon, participant sex, severity of incontinence and degree of anal sphincter defect. The technique for FENIX implantation was standardised according to the manufacturer's guidance, whereas the technique of sacral nerve stimulation was left to the surgeon's normal practice. Data were captured at baseline, 2 weeks post intervention and at 6, 12 and 18 months post randomisation. The Cleveland Clinic Incontinence Score was used to assess incontinence and the Obstructed Defaecation Score was used to assess constipation. Quality of life was assessed by participant-reported questionnaires, using the faecal incontinence quality of life, EuroQol-5 Dimensions, five-level version and Visual Analogue Scale, and SF-12 questionnaires. In addition, participants completed the Health and Social Care Resource Use questionnaire.

All analyses were prespecified and conducted on an intention-to-treat basis. The results are reported with 95% confidence intervals and *p*-values for fixed effects. For all end points, missing outcome data were assumed to be missing at random, and the treatment effect was estimated via maximum likelihood estimation using all participants with non-missing outcome data for non-longitudinal end points. A sensitivity analysis of the primary end point was performed considering other covariates thought to be related to participant outcome. All modelling was performed using SAS® (SAS Institute Inc., Cary, NC, USA) version 9.4 glimmix procedure.

The economic evaluation was from the perspective of the social and health-care provider generating cost per quality-adjusted life-year over a lifetime horizon. We analysed trial cost and quality-adjusted life-year data and extrapolated these forward using a de novo decision-analytic model.

Results

The study was prematurely stopped in 2017 when the manufacturing company was bought by a multinational company and the FENIX device was withdrawn from the market. Between 30 October 2014 and 23 March 2017, 322 participants were assessed for eligibility; 23 participants were registered as training cases, and 99 participants were randomised into the study (50 FENIX and 49 sacral nerve stimulation). The baseline characteristics of the two groups were similar and in keeping with a population suffering from moderate to severe faecal incontinence. The median time from randomisation to FENIX implantation was 57.0 days (range 4.0–416.0 days). The median time from randomisation to temporary sacral nerve stimulation was 86.5 days (range 2.0–699.0 days) and the median time from randomisation to permanent sacral nerve stimulation was 371.0 days (range 86.0–918.0). Five out of 50 participants did not undergo FENIX implantation, and 5 out of 49 participants did not undergo temporary sacral nerve stimulation. A total of 32 participants continued to permanent sacral nerve stimulation, of whom three did not have a device implanted. For the primary end-point analysis, 19 participants had missing data, meaning that there was complete data available for analysis for 80 out of 99 (80.8%) participants.

Overall, there was success for 10 out of 80 (12.5%) participants, with no statistically significant difference between the two groups [FENIX 6/41 (14.6%) participants vs. sacral nerve stimulation 4/39 (10.3%) participants]. A longitudinal analysis using data obtained at 6, 12 and 18 months post randomisation did not show a statistically significant difference between the treatment groups, with no significant difference over time.

There were four intraoperative complications in four participants: three during FENIX implantation and one during implantation of a permanent sacral nerve stimulation. A total of 42 out of 85 participants experienced at least one postoperative complication: 33 out of 45 (73.3%) in the FENIX group and 9 out of 40 (22.5%) in the sacral nerve stimulation group. The adjusted odds ratio revealed a statistically

significant difference between the two treatments (11.21, 95% confidence interval 2.65–47.35; $p = 0.004$). A total of 15 out of 50 (30%) of the FENIX devices were explanted, usually within 6 months; there were no explants in the sacral nerve stimulation group.

Data were available from 96 out of 99 (97%) participants for analysis of the secondary end point: the Cleveland Clinic Incontinence Score . The results showed that having a device in use led to a statistically significant reduction in the Cleveland Clinic Incontinence Score of 3.04 points, but with no difference observed between the treatment groups. The quality-of-life analysis using the EuroQol-5 Dimensions, five-level version questionnaire showed a statistically significant improvement in quality of life in participants with the device in use (EuroQol-5 Dimensions, five-level version score 0.13 higher; $p = 0.004$), with no difference between the treatment groups. This finding was not replicated in the analysis of the Visual Analogue Scale score, with the randomised treatment producing no benefit and no difference observed between the treatment groups over time. Analysis of faecal incontinence quality of life showed a statistically significant improvement across all four domains when the device was in use, but no significant difference between the treatment groups. Despite obstructed defaecation being the most commonly reported complication following FENIX implantation, no significant difference was observed between the treatment groups, and whether or not a participant had a device in use did not produce a statistically significant difference in the Obstructed Defecation Score. The benefits of having a device in use appeared to be due to improvements in physical component scores rather than mental component scores, as assessed by the Short Form questionnaire-12 items, with no differences between the treatment groups.

At the end of the trial period, slightly higher costs and quality-adjusted life-years (incremental = £305.50 and 0.005, respectively) were observed in the FENIX arm. The sample size available for the analysis limits our ability to draw robust conclusions. The trial results were reversed over the lifetime horizon (incremental = −£1306 and −0.23 for costs and quality-adjusted life-years, respectively) with sacral nerve stimulation being the optimal option (net monetary benefit = −£3283). These analyses were relatively robust to deterministic sensitivity analyses; however, there was significant uncertainty, with sacral nerve stimulation having only a 55% chance of cost-effectiveness over a lifetime. Given the small sample sizes available for parameter value generation, caution is needed in interpreting the results.

Conclusions

Interpretation of the results is limited because of the early termination of the study, which means that the numbers available for analysis are small, with a high proportion of participants in the sacral nerve stimulation group not undergoing permanent sacral nerve stimulation implantation or not completing the 18-month follow-up. With this caveat, the rates of success for both FENIX and sacral nerve stimulation are disappointing and much lower than previously reported in the literature. The complication rates associated with the FENIX device are high, with around one-third of participants undergoing explantation. For those participants for whom a device remained in use, there were benefits in terms of improvement in continence score and quality of life. Based on the cost-effectiveness analysis, if the FENIX device were still available, it is uncertain whether or not it would be recommended for routine use in patients with faecal incontinence given the costs associated with complications.

Trial registration

This trial is registered as ISRCTN16077538.

Funding

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 18. See the NIHR Journals Library website for further project information.

Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.370

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 12/35/07. The contractual start date was in January 2014. The draft report began editorial review in June 2019 and was accepted for publication in October 2020. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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