# Clinical effectiveness of subsensory sacral neuromodulation in adults with faecal incontinence: the SUBSoNIC crossover RCT and mechanistic study

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# Scientific summary

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# Scientific summary

## Background

Faecal incontinence (FI), defined as the recurrent involuntary loss of faecal material leading to a social or hygienic problem, is a common and debilitating condition with profound effects on quality-of-life and high societal costs. Initial treatments including pharmacological and behavioural therapies (e.g. biofeedback) have variable outcomes and are poorly evidenced. Traditional surgical approaches focusing on anal sphincter reconstruction or augmentation are invasive, irreversible, and risk significant morbidity. A stoma is the final option.

Chronic low-amplitude stimulation of the mixed sacral spinal nerves using an implanted electrode and pulse generator – sacral neuromodulation (SNM) is a less invasive alternative, now considered the first-line surgical treatment option for adults with FI in whom non-operative therapies have failed to alleviate symptoms. Current evidence for SNM is based on extensive observational data and few randomised trials that are heterogeneous in design and outcomes. Despite having widespread regulatory approval, SNM remains an expensive intervention with need for greater confidence in efficacy. A further concern regarding SNM therapy is the lack of evidence and understanding of the mechanism of any effect.

## Objectives

Our primary aim was to determine the clinical efficacy of sub-sensory chronic low voltage electrical SNM using a commercially-available implantable device in adults with FI in whom conservative treatment has failed. We sought to determine whether SNM, compared to sham, led to a clinically important reduction in weekly FI episodes.

The study also included mechanistic studies to examine whether clinical responses to sub-sensory SNM were biologically related to changes in the central pathway between the brain and anorectum.

## Methods

### *Trial design*

SUBsensory Sacral Neuromodulation for InContinence (SUBSoNIC) was a multicentre, randomised double-blind crossover trial at nine UK sites and one site in Ireland in which SNM was compared to sham stimulation. We aimed to randomise 90 eligible participants (adults aged 18–80 years, where non-surgical approaches to National Institute for Health and Care Excellence (NICE) standard have failed and meeting minimum FI severity criterion) to two study arms after SNM implantation. Both arms had two intervention periods (ON-OFF or OFF-ON) of 16-week duration (T0–T16 and T16–T32). Efficacy outcomes were derived from assessments in the final 4 weeks of each cross-over period (T12–T16 and T28–T32) thus allowing for almost 3 months intervention before outcome assessments (and adequate washout for participants in the ON–OFF sequence). Mechanistic studies were performed in the final 2 weeks of the 4-week assessment periods in a subgroup of consecutively consenting participants from both arms until data saturation.

After completing the crossover phase of the study, participants were followed up for a further 26 weeks. During this time, participants had either sub- or supra-sensory 'open label' stimulation based on preference as would have been normal for routine clinical practice. Further efficacy outcomes were recorded at T54–T58 to provide an indication of the short-term effectiveness of SNM within the rigor of a clinical trial unit (CTU)-monitored prospective study.

### *Interventions*

Chronic low voltage stimulation of the third or fourth sacral root was achieved by surgical implantation of a commercially available Conformité Européenne-marked active implantable (class III) medical device [Medtronic InterStim™ (Medtronic, Minneapolis, MN, USA)] used in accord with the manufacturer's instructions and local practice. For the active intervention (ON), the clinical team programmed the device using standard settings of a 14-Hz frequency and 210-μs pulse width. Optimal electrode configuration was determined by cumulatively increasing the amplitude of stimulation by 0.1 V from zero for each electrode until the sensory threshold was reached. The amplitude and site of stimulation were recorded for each electrode with the electrode configuration that achieved sensation in the anus or perineum at lowest amplitude being chosen for chronic stimulation. Sub-sensory chronic stimulation was initiated by reducing the amplitude to a level just below the habituated sensory threshold (for blinding). For the sham intervention (OFF), sensory thresholds were recorded identically; however, the level was then adjusted to zero volts or 0.05 V (the latter was required in some participants due to the new device handset limitations).

Mechanistic studies were undertaken at the Institute of Health and Neurodevelopment (IHN) at Aston University in a subgroup of patients identified in the Midlands region (compared to 20 healthy volunteers without FI). A protocol including spatial registration (magnetic resonance imaging head) and a series of magnetoencephalographic (MEG) acquisitions measured induced and evoked cortical activity relevant to determining functional connectivity between the anus and brain (using anal electrical stimulation) and brain and anorectum (using volitional anal squeeze). Control paradigms (tibial nerve stimulation and fist clench) were used respectively.

### *Outcomes*

The primary clinical outcome was reduction in FI events per week (recorded on paper bowel diaries over a 4-week period) in SNM versus sham phase of crossover (16 and 32 weeks). Secondary clinical outcomes including other bowel diary measures, e-event recording and a panel of summative questionnaires were recorded at 16, 32 and 58 weeks. Mechanistic outcomes included spatial localisation, relative cortical source signal strength and latencies of evoked and induced responses.

### *Allocation and blinding*

Randomised allocation (1 : 1) to group 1 (SNM/sham) or group 2 (sham/SNM) was performed at the time of surgery using an online randomisation system managed by the Pragmatic Clinical Trials Unit at QMUL, with a randomisation list generated by an independent statistician to ensure allocation concealment. Randomisation was stratified by sex and centre with block sizes of four. Members of the research team, statisticians, surgeons who performed the surgical procedure, and participants were blinded to intervention status (SNM or sham). Participants were informed of the allocation ratio of 1 : 1 and that blinding prevented them from knowing in which group they were participating. Tamper-proof tape was used to mask stimulation settings.

### *Sample size and statistics*

The study was designed to detect a mean 30% reduction between SNM and sham stimulation in FI event rate (ratio 0.7). At 90% power and 5% significance level with a cross-over design this required 90 participants (45 per group), allowing for 10% loss to follow-up.

The pre-specified analysis for the primary outcome involved a mixed Poisson regression applied to the counts of FI events, with fixed effects of cross-over period and stratification factors, a random effect of individual, and a random effect of period within individual (the latter to allow for an over-dispersed Poisson distribution). When it came to the analysis, owing in part to the small numbers, the Poisson regression models did not converge for the count outcomes. Instead we applied a paired t-test to the FI rates in order to estimate the difference between SNM and sham with a 95% confidence interval and *p*-value.

## Results

### *Clinical results*

The COVID-19 pandemic had a major effect on trial recruitment and patient retention. The trial was terminated on 24 July 2022 with just 39 patients randomised. Trial delivery was severely affected and terminated early due to COVID-19. Main barriers were the inability to continue face-to-face patient visits, redeployment of research staff to COVID-19 facing clinical roles and cancelling of SNM procedures due to lack of priority for non-urgent surgery. In total, 220 patients were screened for eligibility at nine sites from the UK and one site from Ireland between February 2018 and July 2022. Of these, 155 patients declined study participation or were ineligible due to study specific exclusion criteria. A total of 65 patients were pre-enrolled and consented to the study, of whom 26 did not meet the baseline minimum frequency criteria of FI episodes per week or did not receive an implant. The remaining 39 patients were randomised (arm 1: *N* = 17; arm 2: *N* = 22); however, only 16 completed the primary outcome during both cross-over periods (arm 1: *N* = 9; arm 2: *N* = 7). The remaining 23 participants withdrew from the study (*N* = 12), were excluded on the basis of problems of eligibility (*N* = 5) or did not complete the primary outcome data (*N* = 6: still included in the cohort follow-up phase). A total of 22 participants started the cohort follow-up phase, although 3 of these participants did not complete the final follow-up visit, leaving 19 participants for the 1-year effectiveness assessment.

There were no major differences at baseline between allocated groups. As predicted, about 90% participants were female with mean age about 57 years. Almost all participants reported symptoms of urgency, combined with varying combinations of passive and urge FI. All participants reported previous conservative management for their FI symptoms (as per NICE guidance). Numbers of FI events at baseline were concordant with design assumptions (based on approx. seven events in a 1-week period). Median St Mark's incontinence score was 19 in both groups, indicating severe symptoms (max score 24). E-event recordings were only undertaken by a minority (14/39) of participants.

Test stimulation was performed using a tined lead in 68.6% participants. General anaesthesia was used in 70.6% of procedures and median operating time was 36 minutes (range 30–55 minutes). The lead was positioned in foramina S3 in most participants (91.4%) with some variations in fidelity of siting based on individual electrode responses (only 50% lead placements achieved the ideal published standard of motor or sensory responses for three electrodes < 1V).

Primary outcome showed that compared to sham, SNM led to a non-significant mean difference of < 1 FI episode per week [−0.7, confidence interval (CI) −1.5 to 0.0; $p = 0.06$]. The estimated treatment effect was greater but less precise in the seven participants who had complete e-event data in both periods (−1.5, −3.5 to +0.5; $p = 0.12$). Secondary outcomes showed small (non-statistical and non-clinically significant) but directional changes favouring SNM versus sham. Adverse events were infrequent (*n* = 10), non-serious and expected; most resolved during the study. Blinding was successful in masking allocation based on contingencies of correct perception. Cohort study outcomes (from open-label sub- or supra-sensory stimulation) showed substantial benefit in terms of symptom reduction at 1 year in keeping with published observational studies.

### *Mechanistic results*

A total of 30 patients recruited from the SUBSoNIC study consented to participate of whom only 12 completed the SUBSoNIC clinical study and nine made all three visits to the IHN. The remaining 18 participants contributed to baseline data. There were small statistically significant increases in electrical stimulus amplitude required for tibial evoked cortical responses between FI patients and healthy controls but no differences in latencies (although these were often numerically longer in patients). Anal electrical stimulation produced measurable evoked potentials in the primary somatosensory cortex near the vertex; however, these did not significantly differ between patients and controls in relative amplitude or latency. Induced motor MEG activity was demonstrated throughout the whole

sensorimotor strips bilaterally during voluntary fist clenching and anal squeezing activity in both patients and controls at 14–30 Hz (beta band). Given the lack of difference between healthy and FI participants, it was difficult to interpret variations seen between SNM and sham periods in the trial.

## Conclusions

Despite very important caveats of under-recruitment (39 of 90) and attrition (only 16 with complete data), SUBSoNIC is the first randomised study of SNM in a treatment naïve population with proven effective double blinding. Due to the under-recruitment it is important to interpret the findings as exploratory. The mean difference in effect between SNM and sham (−0.7 FI, 95% CI −1.5 to 0.0, episodes perweek) represents a mean percentage reduction of 23.3% (0.7/3.0) when expressed with reference to sham frequency. This effect is less than that sought by the predetermined sample size calculation (0.77 vs. 0.70) and much less than the placebo response (possible placebo effect) based on symptom frequency reductions of a 50% reduction between baseline and sham. Differences in reporting between the paper bowel diaries and the e-event recording re-emphasise the importance of how FI outcomes are measured and the frailties of current approaches.

## Future work

Since the primary objective of the SUBSoNIC trial remains relevant and unanswered, future studies could seek to repeat SUBSoNIC in a post-COVID era. Attention should be paid to improving on current estimation of clinical effect by outcomes research and strict curation of source observations during trial delivery. Placebo 'effects' from SNM merit further clinical and mechanistic evaluation.

## Study registration

Current Controlled Trials ISRCTN98760715.

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## This article

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