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Title page

The short-term false positives after sacral neuromodulation therapy: Who, how many and why? A prospective descriptive single centre study.

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Abbreviations:

AE	Adverse events
BS	Bowel symptoms
CRD	Colorectal Surgery Department
FP	False positives
FSTLP	First Stage Tined-Lead Placement
IPG	Implantable Pulse Generator
LUTD	Lower urinary tract dysfunction
OAB	Overactive bladder Syndrome
ObS	Objective success
PGIC	Patient Global Impression of Change Score
PNE	Percutaneous Nerve Evaluation
PROMS	Patient Reported Outcome Measures
SNM	Sacral neuromodulation
TP	True positives
UD	Urology Department
US	Urological symptoms

Abstract

Aim: I. To describe the number of false positive cases (FP), their characteristics and reason of occurrence in sacral neuromodulation therapy (SNM).

Methods: A multidisciplinary prospective single-centre study was conducted between March 2018 and December 2021 with a follow-up of 12 months. Patients with therapy-resistant pelvic organ dysfunctions, scheduled for a 2-staged SNM procedure at the Urology (UD) and Colorectal Surgery Department (CRD), were included. All patients completed bowel and bladder diaries at baseline and during the test phase. Patient global impression of change (PGIC) and satisfaction scores concerning urological (US) and bowel symptoms (BS) were surveyed at baseline, at 1, 6 and 12 months after implantation. Patient characteristics and diary outcomes between FP and true positive cases (TP) were compared using non-parametric statistical tests. SPSS 27.0 was used. Clinical trial registration: NCT05313984.

Results: The FP ratio at one month follow-up was 16% (11/68), with a FP ratio of 13% (N=6/48) and 25% (N=5/20) for the urology patients and colorectal surgery patients, respectively. There were no significant differences in demographic characteristics between the FP and TP group (p>0,05), however there is a trend towards FP having worse baseline symptoms than TP. The FP group had a significant lower baseline and test phase 24hours diuresis (p<0,05), without having a significant different intake than the TP group.

Conclusion: At one month after full implantation of a sacral neuromodulator, 16% of the patients showed loss of subjective success. These FP could not be predicted from demographic characteristics, most likely due to the small study population. Although not significant, FP seem to have worse symptoms at baseline than TP, with a significant lower diuresis regardless of fluid intake.

Key words: Sacral neuromodulation, pelvic floor, incontinence, placebo effect, diuresis.

1. Introduction.

Over the last decades, sacral neuromodulation (SNM) has been a widely accepted 3rd-line therapy for bladder and bowel-dysfunctions refractory to conservative treatments. Food and Drug Administration approved indications are urgency-frequency, urgency urinary incontinence, chronic non-obstructive urinary retention and faecal incontinence.[1] Although the off-label single stage Direct-To-Full implantation (DTFI) technique[2] would have many advantages for the patient by reducing the surgery and anaesthesia-related risks, the two-phased technique currently remains the golden standard.[1] Hereby, the test phase (i.e. Stage I) precedes the implantation of an Implantable Pulse Generator (IPG) (i.e. Stage II) and allows the assessment of the clinical and subjective efficacy before deciding to implant an expensive device. Stage I is either performed by a Percutaneous Nerve Evaluation (PNE) test using a temporary electrode, or by a First Stage Tined-Lead Placement (FSTLP) test using a permanent electrode.

Not only for the patient, but also with regard to cost-effectiveness, appropriate patient selection for a definitive implant is crucial. Ideally, screening of subjective success and objective success (ObS) is performed by the evaluation of standardized patient reported outcome measures (PROMS) and an accurate analysis of bladder and/or bowel diaries, as standard of care prescribes. Patients who achieve the arbitrary determined ≥ 50% cut-off of improvement in at least one bothersome baseline urinary or bowel parameter during the test phase, may be offered a complete implant.[1]

Conversion ratios from first stage to full implant have been reported to be around 80% for refractory lower urinary tract dysfunctions (LUTD)[3] and 80-90% for bowel indications.[4,5] Long term ObS ratios vary between 70%-80% for LUTD[6,7] and around 60 % for faecal incontinence.[8,9] Hence, therapy failure can occur in a variable degree after a certain timespan. The occurrence of an event such as lead migration, accidental damage of the prosthesis material, battery deprivation or habituation to stimulation can be reasons for failure at any time. Nonetheless, short term failures in the absence of such an event can occur as well. We state that, if appropriate patient screening by accurate analysis of ObS and subjective success during the test phase is performed, but therapy failure still do occur on the short term in the absence of an event, it should be denominated as a 'false positive case'. In literature this is not yet nominated as such. The aim of this study was to characterize the false positive

cases (FP) (who), describe the FP ratio (how many) and ultimately to formulate a possible explanation for their occurrence (why) by analysis of their demographic variables and diary variables.

2. Materials & methods:

2.1 Study design

As part of research phase I of the OptiLUTS project Part C, a prospective single centre study was conducted between March 2018 and December 2021. The protocol of the OptiLUTS project has been published previously.[10]Approval for this project was obtained by the Ethics Committee of the Ghent University Hospital in March 2018 (EC/2018/0244). This trial is a report on data from 1 month, 6 months and 12 months follow-up.

2.2. Patients

Patients referred for pelvic organ dysfunctions to the Urology department (UD) and Colorectal Surgery department (CRD) of the Ghent University Hospital who were scheduled for a 2-staged SNM procedure using Interstim™ II therapy (Medtronic, Inc., Minneapolis, USA) were enrolled. Inclusion criteria were subjects ≥ 18 years presenting with one or more of the following indications: urinary urgency frequency with or without urinary incontinence (OAB dry or wet), non-obstructive urinary retention, dysfunctional voiding with post void residual volume, faecal incontinence and mixed incontinence refractory to conservative treatment, including pharmacotherapy. Patients with a neurogenic bladder, anal sphincter damage more than 120°, abnormal sacral anatomy, mental or physical disabilities not capable to handle a patient programmer device or pregnant patients were excluded. Patients who didn't complete the required outcome data (bladder and bowel diaries and patient reported outcome measures (PROMs) at the key time points (at baseline, during the test phase and at one month follow-up) were excluded. A written informed consent from all participants was obtained.

2.3 Procedure

At baseline, all subjects were requested to complete a modified 3-day bladder diary (ICIQ-Bladder diary)[11] including a numeric rating scale (NRS) for lower urinary tract pain and a 3 week bowel diary, including a Wexner score.[12] Additionally, a NRS concerning the degree of satisfaction with the current situation from 0% (Not

satisfied at all) to 100% (Completely satisfied) for both urological symptoms (US) and bowel symptoms (BS) was asked, as well as the 36-Item Short Form Health Survey (SF-36), scored from 0 (maximum disability) to 100 (no disability).

The first stage tined lead procedure (FSTLP) of Interstim™ II Therapy (the Advanced Evaluation System) was performed according to the Standardized Electrode placement technique as previously described.[13] As recommended by various authors, the curved stylet lead was used.[14,15] Experienced surgeons, 4 urologists (in case of a UD patient) and one colorectal surgeon (in case of a CRD patient) performed the surgery. Patients who were considered as successful at the test phase by the treating surgeon, received a full IPG implant (Model 3058). As Belgian law foresees in case of substantiated clinical and subjective success, reimbursement was fully provided.

2.4 Assessment of test phase by the physician

After the FSTLP, a test period of 1-2 weeks for the UD and 3-4 weeks for the CRD followed. The same set of diaries and satisfaction scores were completed, as well as the 'Patient Global impression of Change' (PGIC) score[16,17] as another PROM for subjective assessment of therapy.

Under the current patient screening strategy of the trial centre, the decision to proceed from Stage I to Stage II was accomplished by the treating physician based on a quick, rather intuitive screening for changes in bladder and bowel diary variables and patient satisfaction, without using standardised questionnaires. In case of doubt, the test phase was prolonged by 1 week.

2.5 Assessment of the test phase by the researcher

As a quality control on the treating physician's advice for implant, a mathematical re-analysis of bladder and bowel diaries was retrospectively performed by an independent researcher, determining the true success ratio (i.e. having both ObS and subjective success during the test phase) of the evaluated patients. According to the recommendations on standard of practice in SNM[1], ObS is defined as having ≥ 50% improvement in at least one of the most bothersome voiding and/or bowel diary variables related to each pathology (See Table 1). In case of

concomitant BS in urological patients and vice versa, 50% improvement in a bothersome variable in one of both domains was also counted as ObS. In this study, subjective success was defined as a PGIC score of ≥ 5 on a scale from 1 to 7 (5: 'Moderately better and a slight but noticeable change', 6: 'Better, and a definite improvement that has made a real and worthwhile difference', 7: 'A great deal better, and a considerable improvement that has made all the difference'). Whether a patient was categorized under true success, was not communicated to the treating surgeon to avoid bias in their advice for implant. After the decision for implant was made by the treating physician, patients were categorized in 4 groups by the independent researcher: 'Incorrectly implanted' in case a patient received a positive advice for implant despite having no true success, 'correctly implanted' in case a positive advice for implant was given for a patient with indeed true success, 'incorrectly refused' in case of a negative advice for implant despite having true success and 'correctly refused' in case of a negative advice for implant was given for a patient with indeed no true success.

2.6 Assessment at one month after the IPG implant

Independent from the assessment of the treating physician, patients were categorized into outcome groups according to their true success during the test phase and the PGIC score at 1 month follow-up. TP were defined as patients with both ObS and subjective success according to the above defined criteria during the test phase and with sustained subjective success (PGIC ≥ 5) 1 month after full implant. FP were defined as patients without sustained subjective success, i.e. a PGIC score < 5 (1: 'No change or worse', 2: 'Almost the same', 3: 'A little better', 4; 'Somewhat better'), in spite of having shown true success.

2.7 Outcomes

Primary outcomes were: the FP ratio at 1 month and the FP's baseline demographic and clinical characteristics, baseline and test phase key diary outcomes, the absolute changes from baseline (including the 24 hour diuresis adjusted for fluid intake (=24 hour diuresis/24 hour fluid intake)) compared to TP. The secondary outcomes were: SF-36, US and BS Satisfaction scores at baseline, during the test phase and at 1 month follow-up, both groups compared. In the total group sustained success and SF-36 scores at 6 and 12 months follow-up were explored.

2.8 Statistics

Statistical analyses were performed using SPSS Statistics 27. Outcome measures were reported as median values (interquartile ranges (IQR)) and median absolute changes (IQR) from baseline measures. The Wilcoxon Signed Rank test was used for comparison of non-parametric distributed baseline versus test phase measures. The Mann-Whitney U test was used for the comparison of absolute change from baseline measures between the FP and TP group. Missing values were not imputed and excluded test-by-test. Univariate logistic regression was used to explore an association between the 24h diuresis adjusted for fluid intake and the outcome group (TP vs. FP). P-values < 0,05 were considered statistically significant.

3. Results

3.1 Descriptive statistics

Figure 1 provides an overview of the study flow from inclusion till the end of the trial at 12 months follow-up. In total 93 patients, median age 52 years (44-64) and 82% female, completed the required data. A total of 82% received a full implant, with an equal implantation ratio of 53/65 (82%) and 23/28 (82%) for the UD and CRD, respectively.

3.1.1 Assessment after stage I.

Re-analyses of data showed a true success ratio of 76% (71/93). Fourteen out of 93 patients (15%) were correctly refused, while 68 out of 93 (73%) patients got a correct positive advice for implant. Under the current decision strategy of the trial centre, 11/93 (12%) patients were incorrectly assessed. The incorrectly refused patients were complex cases who did show ObS on their most bothersome key diary parameters, but were refused for practical reasons. Eight patients were incorrectly implanted. All the patients from the UD within this group (5/8), showed ≥ 50% improvement in bowel diary parameters although their original complaint was OAB dry (3/5), OAB wet (1/5) and mixed incontinence (1/5). The other patients from the CRD (3/8) had FI and showed ≥ 50% improvement in bladder diary parameters (Figure 1).

3.1.2 Assessment after stage II.

Baseline demographics and clinical characteristics of the TP and FP are listed in Table 2. No significant differences between TP and FP were seen. The FP ratio and TP ratios were 11/68 (16%) and 57/68 (84%) respectively. FP ratios for CRD patients were higher (5/20) than for UD patients (6/48), although not significant (p= 0,202).

Diary variables outcomes are listed in Table 3. Differences between baseline and test phase outcomes are significant for the majority of both US and BS (p-values[a] <0,05) in the TP group, whereas in the FP group the 24 hour voiding frequency (p=0,041), the number of urgency incontinence episodes a day (p=0,018), the number incomplete bowel attempts/day (p=0,028) and the number active faecal incontinence episodes/week (p=0,042) differed significantly. Baseline diary variables, such as the number of voids/day and average voided volume/void are worse for FP than for TP, although not significant (10 vs 8 voids and 119 ml vs. 194 ml, respectively). No significant differences in absolute changes in test phase variables from baseline are seen between TP and FP (p>0,05).

SNM did not show to have an influence on 24h fluid intake and 24h diuresis in any group. Subgroup analyses of the UD and CRD separately neither showed a significant change in the 24h diuresis during the test phase (Δ=0 ml, p=0,581 for the CRD and Δ=66 ml, p=0,257 for the UD). FP demonstrated to have a lower baseline (p=0,012) and test phase (p=0,025) 24h diuresis and 24h diuresis adjusted for fluid intake (p=0,020) than TP. Although not significant, the 24h diuresis adjusted for fluid intake increases after the test phase in FP, whereas in TP not. Univariate logistic regression analysis could not show an association between the absolute change in the 24h diuresis adjusted for fluid intake and a FP outcome (OR: 2,206 95% CI: 0,312 - 15,617; p-value: 0,428).

The median baseline SF-36 score was significantly lower in the FP group; 27 (22-47) on a scale to 100, than the baseline score in the TP group; 52 (35-74) (p=0,020). For both groups, median scores increased significantly during the test phase (p < 0,05); with 11 (1 -21) for the FP and 15 (0,1-75) points for the TP, respectively. Satisfaction on US and BS scores changed significantly during the test phase in the TP group (p < 0,001), whereas in the FP group only the median Satisfaction on BS score did change significantly (p=0,034). FP have a significant worse median baseline Satisfaction on BS score than TP (p=0,031). For none of the PROMS, significant differences in absolute changes from baseline during the test phase were seen between FP and TP. At one month follow-up,

only Satisfaction on US scores compared to baseline decreased almost significantly (p=0,058) among FP, whereas Satisfaction on BS scores stayed stable (p=1) (Figure 2).

Outcomes at 6 months and 12 months follow-up.

Outcomes at 6 and 12 months were characterized by a high number of missings. In the total group of implanted patients subjective success ratios at 6 and 12 months were 76% (32/42) and 85% (35/41), respectively. From the 11 FP, 4/8 (3 missings) at 6 months and 5/6 (5 missings) at 12 months follow-up regained subjective success after reprogramming. Median SF-36 scores at 6 an 12 months were 46 (34 -69) (p=0,015) and 68 (50-86) (p=0,001) on a scale to 100, both significant compared to baseline.

4. Discussion

Despite the importance of FP in terms of cost-effectiveness and patient burden, literature on FP in the field of SNM is scarce. Failure after full implant has been well-described in previous trials, but mostly with regard to clearly identifiable causes or failures on the long term.[3,7] Adverse events (AE) such as undesirable change in stimulation, implant site infection, lead fracture and lead migration have been reported with the consequent loss of efficacy.[7,18] While most AE can be resolved with surgical re-interventions, some will require total removal of the implant. In a prospective series analysing AE within 12 months follow-up, a surgical reintervention ratio of 4% due to loss of efficacy was reported. However, in all cases this loss of efficacy was caused by the aforementioned identifiable AE.[18] In light of the OptiLUTS trial[10] a descriptive study was performed to identify SNM patients who experience short term therapy failure in the absence of an event. To identify these FP, a critical re-analysis of the current screenings strategy was performed. Amongst the 'incorrectly implanted' patients, half of the patients showed improvement in symptoms related to the other discipline than wherefore they received SNM. Almost all of those patients showed sustained subjective success at 12 months follow-up. If a strict application of the definition of success would have been applied, some patients would have been denied treatment from which they do benefit from on the long term. This finding emphasizes the need for a more personalised patient centred and multidisciplinary approach when considering SNM.

The aim of our trial however was to describe the number of FP in our cohort, their characteristics and possible explanations for their occurrence. The table below provides a summary overview of the 'who, how many and why' of false positives.

'Who, how many and why' of false positives after SNM.		
	Observations	Conclusion
Who?	1. The group of FP consists of 5 CRD and 6 UD patients. Among them 4 OAB wet, 1 OAB dry, 1 NOUR, 3 FI and 1 mixed incontinence patient. 2. TP and FP do not differ significantly in demographic characteristics. 3. FP have a significant lower baseline SF-36 score and Satisfaction on BS score than TP.	1. The FP group is heterogeneous. 2. FP are not predictable by demographic characteristics. 3. FP seem to have worse symptoms and a lower general health status at baseline than TP.
How many?	1. The FP ratio is 16 % (N=11/68) with a FP ratio of 25% for CRD (N=5/20) and 13% (N=6/48) for UD patients. 2. Among those FP, 5 patients regained subjective success after reprogramming, 1 did not. 5 responses were missing.	1. The rate of FP is higher among CRD patients than among UD patients, although not significant. 2. Reprogramming after definitive implantation can reduce the number of FP. The ones who regain subjective success should therefore be considered as 'false' FP.
Why?	1. Absolute baseline diary variables (both US and BS) seem worse for FP than for TP, however not significant. Only the baseline and test phase 24h diuresis is significantly lower in FP than in TP, without significant differences in fluid intake. 2. The 24h diuresis adjusted for fluid intake increases after the test phase in FP, although not significantly.	1. FP seem to have worse symptoms and a lower general health status at baseline than TP 2. FP have a lower baseline 24h diuresis than TP, without drinking less. 3. There is a trend of a steeper curve for FP than for TP in the 24h diuresis adjusted for fluid intake does suggest some influence of SNM on diuresis.

How many?

The number of FP is rather low, but should not be neglected. After reprogramming, this number lowered to only one true FP at 12 months, together with 5 patients who did not adhere to the study until the end of the trial, most likely due to treatment dissatisfaction. Before early explantation or revision is considered, reprogramming should therefore be performed.[19]

Who?

Studies on predictive factors for implant failure have been conducted before, without any conclusive findings. The test phase is up-to-date the only reliable factor in predicting success.[20] Our lack of statistically significant differences in baseline variables between FP and TP, as well as in baseline vs test variables in the FP group, are most likely due to the low number of FP. Nevertheless, the finding that FP have a worse overall self-reported health status than TP and that there is a tendency towards worse diary symptoms, are remarkable and warrant for further research with a larger study population. People with worse symptoms at baseline should deserve elaborate attention in the test phase assessment.

Why?

In search of the aetiology of FP and thus differences between FP and TP, of all diary variables only a significant lower baseline 24h diuresis and baseline 24h diuresis adjusted for fluid intake could be remarked among FP. Apart from non-controllable factors such as sweating, insensible losses, cardiac and renal function, FP might adapt their dietary intake to prevent provocation of urinary incontinence and bowel symptoms. Moreover, since bowel symptoms at baseline are significantly worse among FP, fluid loss due to faecal incontinence is not unlikely.

During the test phase, the 24h diuresis adjusted for fluid intake tended to increase more in FP than in TP, suggesting some influence of SNM on diuresis among FP. We hypothesize that a certain placebo effect might could play a role in this mechanism. Clinical trials have shown the existence of the placebo effect in surgical procedures.[21] For SNM however, pure RCT's are complex to perform and scarce which implies that an underlying placebo effect in SNM therapy cannot be completely ruled out. A double-blind crossover trial by Leroi et al., randomizing patients in consecutively an ON and OFF stimulation period, did show a significant preference of the patient for the ON period. The authors concluded from these findings that the clinical benefit of SNM was not due to a placebo effect.[22] In a more recent double-blinded controlled trial by Liechti et al.[23], patients with a full implant with proven therapeutic efficacy were randomized in a SNM ON and OFF stimulation group after 2 months of subsensory stimulation. Still 42% of the control patients (SNM OFF group) showed therapeutic success after 2 months without stimulation vs. 76% of the SNM ON group. The authors attributed this positive effect to a prolonged effect of SNM. In our opinion, the clinical benefit of active therapy over sham therapy, does not rule out a potential placebo effect. In fact, it is consented that the total active treatment outcome is always a

combination of an active treatment effect and a placebo effect[24], whereby not only psychological responses can lead to the perception of improvement, but also physiological changes can lead to objective improvement.[21] From this point of view, we hypothesize that the placebo effect, principally dopamine driven[11], might could lead to measurable physiological changes in the SNM population as well, such as impacting diuresis. The effect of dopamine on diuresis is complex. On central level, dopamine infusion would increase Atrial natriuretic peptide (ANP) in healthy volunteers.[25] On peripheral level, intrarenal dopamine acts as a regulator of proximal tubule salt and water reabsorption through interaction with D1-like receptors and D2-like receptors. Administering low dose exogenous dopamine in healthy volunteers stimulates these receptors inducing natriuresis and enhances renal blood flow by renal vasodilation.[26,27] Derived from both findings and hypothesizing that FP at the short term might be attributable to a placebo effect, we could expect to remark an increased diuresis in FP during the test phase. Although this finding was not significant, a tendency towards increased 24h diuresis adjusted for fluid intake among FP was seen.

In order to explore the role of diuresis and placebo in SNM, an ideal study design would imply a true placebo controlled SNM trial where diuresis is strictly measured in both the intervention and placebo arm, thereby registering influencing factors. McAlees et al. set up a protocol for a genuine RCT comparing subsensory sacral neurostimulation with sham stimulation in a faecal incontinence population.[28] Although only bowel specific parameters were registered, the inclusion of urological parameters such as diuresis in a setting of non-urological patients would form the ideal opportunity to exclude confounding factors from urological indications. In this trial however, sub-analyses on CRD patients only did not show a significant association between diuresis and a false positive outcome either. Amongst others, dietary intake, physical activities and diuresis influencing comorbidities should be incorporated as confounding factors in future studies to examine the true predictive value of diuresis change in FP.

This study was limited by the absence of repeated diary measures after stage II. However, in the real clinical setting patient satisfaction is eventually the most important outcome after full implant. Requesting patients to complete diaries after stage II, would have lowered study participation and increased missing data. Performance bias cannot be excluded as the surgery and therapy assessment was performed by different surgeons. Moreover, surgical experience differed and some might have used other criteria for decision-making, implying different

outcomes. Also, patient expectation patterns regarding the surgery outcome might have differed due to performer's heterogeneity and it is known that expectation plays a key factor in the placebo effect.[24]

Further research is needed to define and examine the phenomenon of FP. In the ideal setting an RCT comparing sub-sensory SNM vs. sham therapy in a large cohort should be set up to examine the impact of SNM on diuresis and whether changes in diuresis can be used as a predictor for FP. Standardized counselling on expectation patterns regarding success ratios and performance and assessment of stage I by the same surgeon should be introduced to avoid bias. Although our findings lack robust conclusions, this trial might trigger others to further explore the phenomenon of FP in SNM.

5. Conclusion

No predictive factors to distinguish FP from TP could be withdrawn, as our study group was small and heterogeneous. However, a tendency towards worse baseline diary symptoms and self-reported health status was seen in FP. FP patients had a lower diuresis at baseline and during the test phase compared to TP, without drinking less. In future studies, new hypotheses on SNM affecting diuresis through a potential placebo effect should be further explored.

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7. Tables

Table 1: Key diary variables during the test phase assessment.

Department	Indication	Key variables (Mean of 3 days Bladder diary or mean of 3 weeks bowel diary)
Urology department	OAB wet	• ≥ 50% improvement in: number of voids per day (24h), average voided volume, number of urgency urinary incontinency episodes per day, number of pads replaced per day. (1,2) Or • Reduction in median bladder sensation score (scale from 1-5) with 1 rank. Or • Reduction of number of voids per day to normal; < 8 voids/d.
	OAB dry OAB dry + bladder pain	• ≥ 50% improvement in: number of voids per day (24h), average voided volume. (1,2) Or • Reduction in median bladder sensation score (1-5) with 1 rank. (1) Or • Reduction of number of voids per day to a normal amount; < 8 voids per day. Or • ≥ 50% improvement in maximal pain score on a numeric rating scale from 0-10.
	Non-obstructive urinary retention Dysfunctional voiding Fowler syndrome	• ≥ 50% improvement in: Number of intermittent catheterizations/day, average intermittent catheterized volume/catheterization (1,2), total catheterized volume per day, unsuccessful micturition attempts, spontaneous voids/day, average voided volume or median bladder sensation score (1-5).
Colorectal surgery department	Faecal incontinence	• ≥ 50% improvement in: Number of active faecal incontinence episodes/week, number of passive faecal incontinence episodes/week (3) or number of pads replaced per day. Or • ≥ 50% improvement in the Wexner score (scale 0-20). Or • ≥ 50% improvement in the number of unsuccessful defaecation attempts or incomplete defaecation attempts.
Urology + colorectal surgery department	Combined urinary + faecal incontinence.	• ≥ 50% improvement in: number of voids per day (24h), average voided volume, median bladder sensation score, urgency urinary incontinency episodes or number of absorbent pads replaced per day. Or • ≥ 50% improvement in: Number of active faecal incontinence episodes/week, number of passive faecal incontinence episodes/week or number of absorbent pads replaced per day. Or • ≥ 50% improvement in the Wexner score (scale 0-20). Or • ≥ 50% improvement in the number of unsuccessful defaecation attempts or incomplete defaecation attempts. Or • Reduction of number of voids per day (24h) to normal; < 8 voids/d.

Table 2: Baseline demographic and clinical characteristics according to group category. (N=68)

	TP (N= 57)		FP (N= 11)		
Variables (Missings)	N (%)	Median (IQR)	N (%)	Median (IQR)	p-value[a]
Age at first stage (y)		52 (44 - 65)		45 (30 - 56)	0,085
Gender (0)					1
Female	49 (86)		10 (91)		
Male	8 (14)		1 (9)		
Department (0)					0,279
Urology department	42 (74)		6 (55)		
Colorectal surgery department	15 (26)		5 (45)		
Indication (0)					0,988
OAB wet	18 (31,6)		4 (36)		
OAB dry	5 (8,8)		1 (9)		
Dysfunctional voiding/ non-obstructive urinary retention	8 (14)		1 (9)		
Fowler syndrome	5 (8,8)		0 (0)		
Faecal incontinence	12 (21)		3 (27)		
Faecal incontinence + urgency urinary incontinence	9 (15,8)		2 (18)		
BMI (2)		26 (23 - 30)		28 (22 - 33)	0,649
Smoking (4)					0,085
Yes	10 (19)		6 (55)		
No	37 (81)		4 (36)		
Diabetes (0)					0,607
Yes	6 (10)		2 (18)		
No	51 (90)		9 (82)		

Conclusion: FP do not differ from TP in demographic and clinical characteristics.

[a]: Independent T-test for continuous variables and Chi-square/Fisher's exact for categorical variables for between-group comparison of baseline characteristics.

Table 3: Outcomes in diary variables: baseline vs. test according to outcome group at 1 month follow-up (N=68).

	TP (N=57)			FP (N=11)			TP vs. FP	
Outcomes (Missings baseline/test)	Baseline	Test	p-value[a]	Baseline	Test	p-value[a]	p-value[b*]	p-value[b**]
Urological symptoms								
24h fluid intake (ml) (0/0)	1560 ml (1124 - 1903)	1650 ml (1650 – 1898)	0,451	1500 ml (1145 - 1718)	1640 ml (956- 1725)	0,859	0,464	0,920
24h diuresis (ml) (0/0)	1733ml (1267 - 2274)	1758 ml (1424 – 2433)	0,376	1028 ml (807 - 1933)	1067 ml (883 - 2150)	0,213	**0,012**	0,868
Adjusted 24h diuresis for fluid intake (0/0)	1,12 (0,86 - 1,37)	1,10 (0,93 - 1,35)	0,94	0,80 (0,66 - 1,17)	0,99 (0,70 - 1,09)	0,477	**0,020**	0,623
N voids/24h (0/0)	8 (6 - 11)	7 (6 - 9)	**0,011**	10 (7 - 14)	8 (6 - 9)	**0,041**		
N voids/night (0/0)	0,7 (0 – 1,3)	0,7 (0 - 1)	**0,038**	0,7 (0-2)	0,67 (0 - 1,67)	0,391		
Average voided volume/void (0/0)	194ml (142 - 247)	227 ml (200 - 289)	**<0,001**	119 ml (50 - 266)	165 ml (80 - 280)	0,328		
Degree of urgency to urinate* (7/7)	3 (2 – 3,5)	2 (2 - 3)	0,096	3 (2- 4)	2 (2 - 2)	0,144		
N urgency incontinence episodes/day (0/0)	1 (0 – 2,7)	0 (0 - 1)	**<0,001**	2,3 (0 - 8)	0 (0 – 1,3)	**0,018**		>0,05
N pads/day (1/0)	0,17 (0 - 2)	0 (0 - 0,67)	**<0,001**	0 (0 - 0)	0 (0 - 0,5)	0,33		
Max. pain score (0/0)	0 (0 - 4)	0 (0 - 0)	**<0,001**	0 (0 - 4)	0 (0 - 1)	0,285		
N catheterizations/day (0/0)	0 (0 – 0,33)	0 (0 - 0)	0,078	0 (0 - 0)	0 (0 - 0)	0,317		
Cath. volume/catheterization (0/0)	0 ml (0 - 50)	0 (0 - 0)	**0,022**	0 (0 - 0)	0 (0 - 0)	0,317		
Bowel symptoms								
Defaecations/week (6/5)	10 (7-19)	9 (7-13)	**<0,001**	7 (5 - 24)	10,5 (6 – 14,5)	0,674		
N non-successful attempts/day (7/8)	0,2 (0 - 0,8)	0,05 (0 - 0,3)	**0,002**	0,07 (0 - 0,9)	0 (0 - 0,2)	0,141		
N incomplete attempts/day (8/9)	0,4 (0 - 1,2)	0,05 (0 - 0,4)	**<0,001**	1 (0,1 - 1,8)	0,2 (0 - 0,6)	**0,028**		
N of urge episodes (9/8)	0,2 (0 - 1)	0 (0 - 0,2)	**<0,001**	0,2 (0 - 1)	0,1 (0 - 0,28)	0,176		
Degree of urgency to defecate** (9/11)	2 (1 – 3)	2 (1 – 3)	**0,013**	2 (2 – 3)	2 (1 – 3)	0,123		>0,05
N active faecal incontinence episodes/week (6/6)	0 (0 - 1)	0 (0 – 0)	**<0,001**	0,2 (0 –1,7)	0 (0 - 0)	**0,042**		
N passive faecal incontinence episodes/week (5/8)	0 (0 - 2)	0 (0 – 0)	**<0,001**	0 (0 – 2,7)	0 (0 - 0)	0,109		
N pads for stool loss/day (9/9)	0 (0 - 1,3)	0 (0 - 0,5)	**<0,001**	0,02 (0 - 2)	0 (0 - 0)	0,068		
Wexner score*** (7/7)	8 (2 - 16)	4 (2 - 7)	**<0,001**	7 (2 -14)	2 (0 - 5)	0,260		

Conclusion:
- TP demonstrate a significant improvement in both urological variables and bowel variables, whereas FP demonstrate only improvement in some.
- FP do not differ from TP in baseline diary variables, neither in absolute changes in diary variables during the test phase.
- 24h fluid intake and 24h diuresis do not change significantly during the test phase.

Baseline 24h diuresis and the adjusted 24h diuresis for fluid intake values are lower among FP.

Outcomes are expressed as medians (IQR). * Degree of urgency to void: range from 1 (Voided out of social reasons) to 5 (severe urgency with urinary loss). ** Degree of urge to defecate: Range from 1 (No urge at all) to 5 (Severe urge with stool loss). *** Score from 0 to 20. The higher the score, worse the symptoms of FI. [a]: Wilcoxon signed rank test for within-group comparison between baseline vs. test outcomes. [b]: Mann-Whitney U Test for between-group comparison of baseline characteristics* and of absolute differences between baseline vs. test outcomes**: p > 0,05 for all variables.

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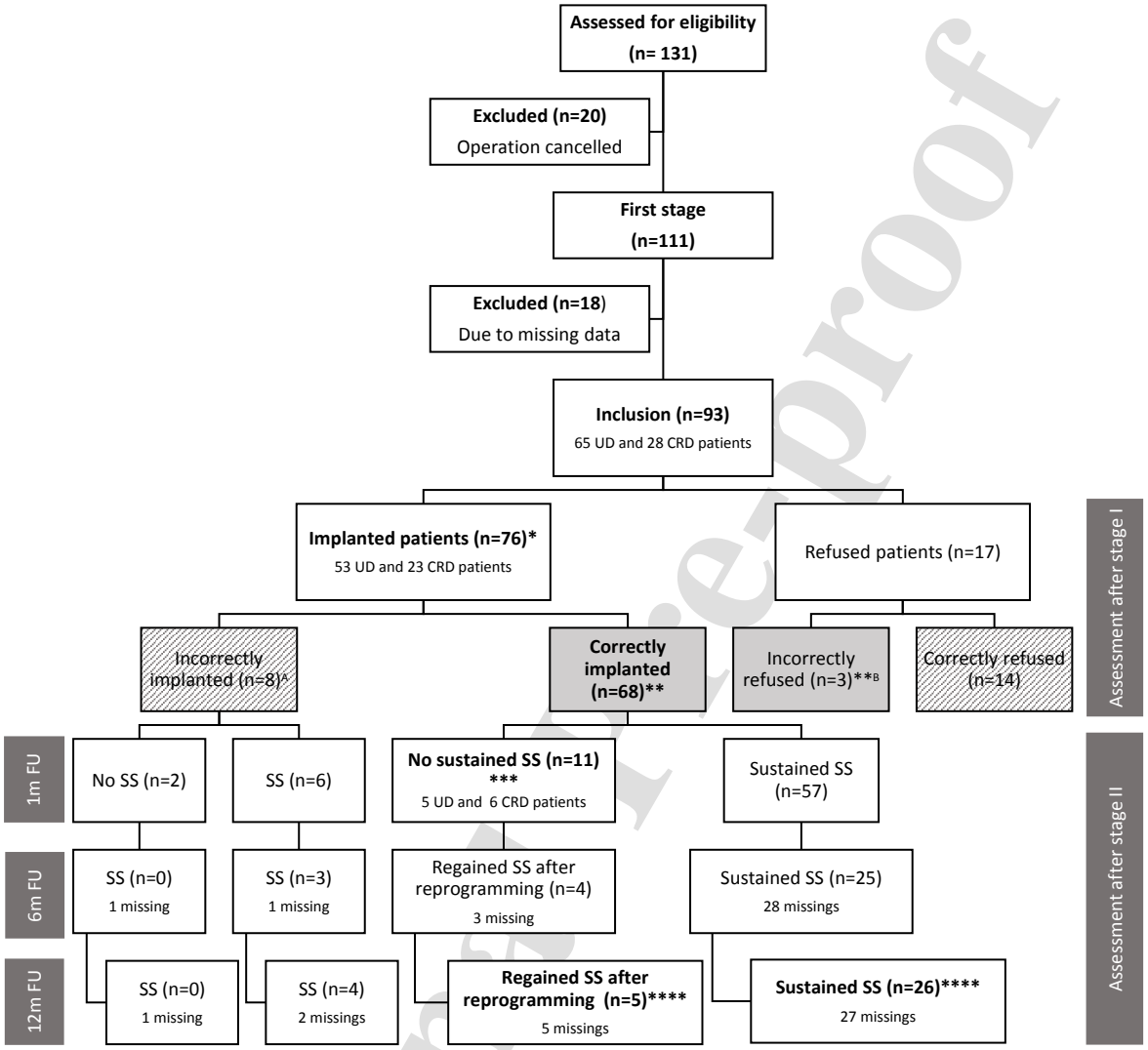
Highlights manuscript '**The short-term false positives after sacral neuromodulation therapy: Who, how many and why? A prospective descriptive single centre study.**'

1. The prevalence of patients with discontinued subjective succes one month after a full implant with sacral neuromodulation therapy (FP ratio) is 16%
2. The occurrence of FP is not predictable by demographic characteristics
3. FP seem to have worse symptoms and a lower general health status at baseline than true positives
4. FP have a lower baseline 24h diuresis than TP, without drinking less.
5. There is a trend towards an increased diuresis, regardless of fluid intake, among FP after SNM

Figure 1. Study flow diagram of the OptiLUTS trial Part C.



Legend

UD: Urology department. CRD: Colorectal surgery department.
x m FU: x months follow-up.
SS: Subjective success = Having a PGIC score of ≥ 5/7.
☐ Having true success = Having objective and subjective success during the test phase.
▨ Not having true success.
[A]: 2 patients (1 UD, 1 CRD patient) showed ObS, but no SS during the test phase. 4/6 (2 UD, 2 CRD patients) did not show ObS on urological symptoms but showing ≥ 50% improvement in bowel symptoms and vice versa. 2/6 (UD patients) showed ObS on urological symptoms, but did not have SS during the testphase.
[B]: 3 patients (2 UD, 1 CRD patient) showing true success, but refused out of practical reasons.

Conclusion
*** Implantation ratio: 76/93 (82%). ** True success ratio : 71/93 = 76%. *** False positives ratio: 11/68 =16%. **** Subjective success at 12 months follow-up: 35/41= 85%.**

Figure 2. Boxplots of urinary and bowel symptoms scores: Evolution over time according to outcome group.

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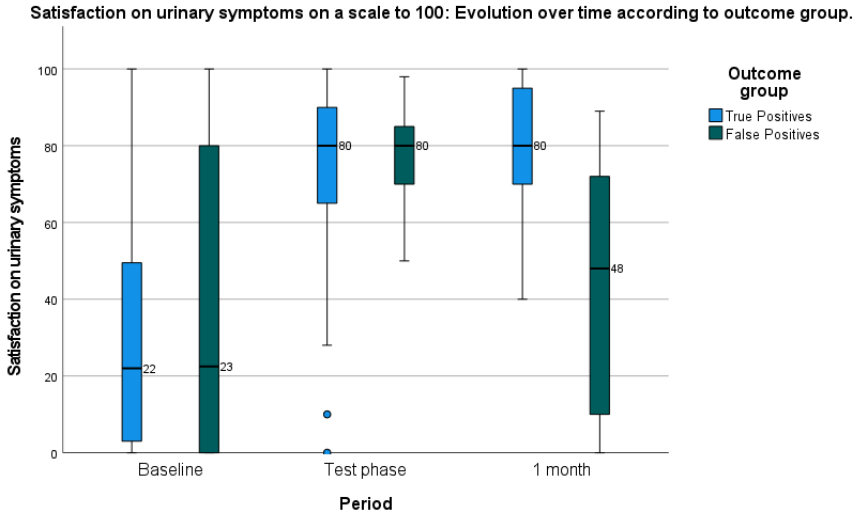

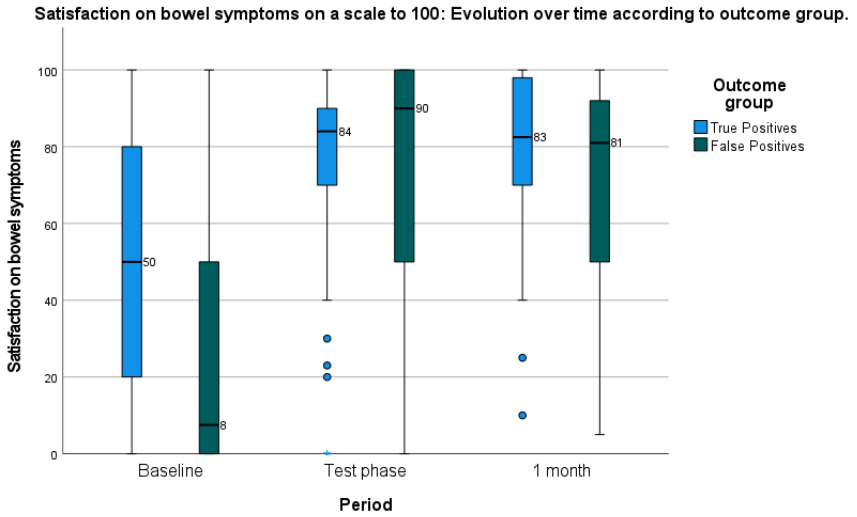

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Lynn Ghijselings reports financial support was provided by Medtronic Inc. Others: Astellas: lecture grant. Kim Pauwaert report a research grant from Ferring. François Hervé reports grants from Astellas, Ferring, Apogepha, Coloplast and Medtronic, outside the submitted work. Prof. Dr. Karel Everaert reports grants and other from Ferring, grants from Astellas, grants and other from Medtronic, outside the submitted work; and is a minority shareholder and co-founder without salary or honoraria of P2Solutions (smart textile applications). The other authors declare that they have no conflict of interests.