Faculty of health Science

Department of Clinical Medicine

# Sacral neuromodulation and injection of bulking agents for faecal incontinence and concomitant pelvic floor dysfunction

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Photo Mona Stedenfeldt

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## Index


**ACKNOWLEDGEMENTS** ..... **2**

**ORIGINAL PUBLICATIONS** ..... **4**

**ABSTRACT** ..... **5**

**NORWEGIAN SUMMARY** ..... **6**

**ABBREVIATIONS** ..... **7**

**INTRODUCTION** ..... **8**

**BACKGROUND** ..... **10**

FAECAL CONTINENCE ..... 10

*The anorectum* ..... *10*

*Defecation* ..... *12*

FAECAL INCONTINENCE ..... 13

*Epidemiology* ..... *13*

*Evaluation* ..... *14*

*Treatment* ..... *17*

FAECAL INCONTINENCE WITH CONCOMITANT PELVIC FLOOR DYSFUNCTION ..... 20

**AIMS OF THE STUDY** ..... **21**

**METHODS** ..... **22**

STUDY DESIGN ..... 22

INCLUSION AND EXCLUSION CRITERIA ..... 24

PROCEDURES ..... 26

*Sacral neuromodulation (SNM)* ..... *26*

*Injection of bulking agent with collagen (Permacol®)* ..... *28*

EVALUATION ..... 29

*Sphincter defects* ..... *30*

*St Mark's score* ..... *31*

*Bowel habit diary* ..... *31*

*Faecal incontinence quality of life scale* ..... *31*

*EQ-5D- 3L* ..... *32*

*ICIQ-UI-SF* ..... *32*

*Sexual function* ..... *32*

PRIMARY AND SECONDARY OUTCOME ..... 33

SAMPLE SIZE CALCULATION ..... 33

RANDOMIZATION ..... 34

BLINDING ..... 34

STATISTICAL CONSIDERATIONS ..... 34

*Additional analysis* ..... *35*

*The CONSORT guidelines* ..... *36*

METHODOLOGICAL STRENGTHS ..... 36

METHODOLOGICAL LIMITATIONS ..... 37

ETHICAL CONSIDERATION, TRIAL REGISTRATION AND FUNDING ..... 38

**RESULTS** ..... **39**

STUDY OVERVIEW ..... 39

*Baseline characteristics of all the participants (n=65)* ..... *41*

PAPER I- PNE ..... 43

*Faecal incontinence* ..... *43*

*Relation between baseline factors and outcome* ..... *43*
*Adverse events* ..... *45*
PAPER II RCT SNM VERSUS PERMACOL® ..... 46
*Faecal incontinence* ..... *47*
*Quality of life* ..... *47*
*Urinary incontinence* ..... *48*
*Sexual function* ..... *48*
*Adverse events* ..... *48*
*Additional analysis* ..... *49*
PAPER III DOUBLE INCONTINENCE ..... 49
*Urinary incontinence* ..... *51*
*Faecal incontinence* ..... *52*
*Quality of life* ..... *52*
*Sexual function* ..... *53*
*Logistic regression model* ..... *53*
SUPPLEMENTARY ANALYSIS NOT PRESENTED IN THE ORIGINAL PAPERS ..... 53
*Predictors SNM (12 months, n=45)* ..... *53*
*Predictors Permacol® (6 months, n=33)* ..... *54*
*Combination of SNM and Permacol®* ..... *54*

**DISCUSSION ..... 55**
PAPER I ..... 55
*Baseline factors and efficacy* ..... *55*
PAPER II ..... 57
*Faecal incontinence* ..... *57*
*Concomitant urinary incontinence* ..... *58*
*Sexual function* ..... *58*
*Placebo* ..... *58*
PAPER III ..... 59
*Double incontinence* ..... *59*
*Sexual function* ..... *60*
*Quality of life* ..... *60*

**CONCLUSIONS AND CLINICAL IMPLICATIONS ..... 61**
*Faecal incontinence* ..... *61*
*Sphincter defect* ..... *61*
*Quality of life* ..... *61*
*Urinary Incontinence* ..... *62*
*Sexual function* ..... *62*

**FUTURE RESEARCH AND PERSPECTIVES ..... 63**

**REFERENCE LIST ..... 65**

**PAPER I-III ..... 74**

**APPENDIX ..... 75**

## ORIGINAL PUBLICATIONS

***Paper I***

Rydningen M, Dehli T, Wilsgaard T, Stedenfeldt M, Kumle M, Lindsethmo RO, Norderval S. *Sacral neuromodulation for faecal incontinence following obstetric sphincter injury – outcome of percutaneous nerve evaluation.*

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***Paper III***

Rydningen M, Riise S, Wilsgaard T, Lindsethmo RO, Norderval S.

*Sacral neuromodulation for faecal and concomitant urinary incontinence following obstetric anal sphincter injury*.

Submitted for publication.

# ABSTRACT

### *Aim*

The overall aim of the PhD thesis was to investigate different aspects of treatment with sacral neuromodulation (SNM) and injection of bulking agents (Permacol®) for faecal incontinence (FI) and concomitant pelvic floor dysfunction in women with a history of obstetric anal sphincter injuries (OASIS).

### *Method*

Consecutive women with severe FI following OASIS after failure of conservative treatment were eligible. All women went through a three-week percutaneous nerve evaluation (PNE) period. The women with a successful PNE, defined as 50 % reduction of weekly FI episodes, were randomly assigned to SNM or Permacol®(1:1). After 6 months, cross over to the other treatment arm were allowed. Baseline factors related to PNE outcome is discussed in paper I. The changes from baseline to 6 months between the SNM group and Permacol® group are analysed in paper II. Outcomes were evaluated with questionnaires for FI (St Mark's score, bowel habit diary), Quality of life (QoL), (Rockwood FIQL, EQ-5D), urinary incontinence (UI) (ICIQ-UI-SF) and sexual function (RooS). The outcome after SNM in women with combined FI and UI (double incontinence, DI) is explored in paper III.

### *Main results*

Fifty-six of the 63 (89%) women had a successful PNE. Efficacy was related to concomitant UI (p=0.046) and body mass index (BMI) (p=0.03). Pain during PNE was related to unsuccessful outcome (p=0.046). The extent of sphincter defect was unrelated to efficacy (p= 0.1). The reduction in the St. Mark's score between baseline and 6 months was 11.2 (SD 5.3) in the SNM group (n=30) versus 2.3 (SD 5.0) in the Permacol® group (n=26), resulting in a difference of 8.9 (95% CI 6.1-11.7, p<0.0001) in favour of SNM. UI ceased in 13 (33%) and weekly FI episodes disappeared in 23 (62%) of the 37 women treated with SNM for DI. The reduction in ICIQ-UI-SF score was 5.8 (95% CI 3.7-8.0, p<0.001) and in the St Mark's score was 10.6 (95% CI 8.6-12.7, p<0.001).

### *Conclusion*

SNM was superior to Permacol® in terms of change in St Mark's score and disease specific QoL. Concomitant UI was successfully treated with SNM in the majority of the women with DI. Outcome was not related to the extent of a pre-existing sphincter defect.

## NORWEGIAN SUMMARY

Det overordnete formålet med studien var å undersøke behandling av alvorlig avføringslekkasje med sakralnervemodulering (SNM) og injeksjon av en romoppfyllende substans (Permacol®) i slimhinnen like innenfor lukkemuskelen. Kvinner med alvorlig avføringslekkasje på bakgrunn av rift i lukkemuskelen i forbindelse med fødsel var aktuelle for studien.

Fra 2012-2014 gjennomgikk 63 kvinner en tre ukers testfase med perkutan nerve-evaluering (PNE). De 56 med effekt under PNE ble videre randomisert til enten SNM eller Permacol®. Effekten på avføringslekkasje, målt med reduksjon i St marks inkontinens-score (0=ingen lekkasje, 24=komplett lekkasje) ble sammenlignet mellom gruppene. Etter 6 måneders fikk de uten effekt tilbud om den andre behandlingen.

I den første artikkelen viste vi at de 56 (89%) kvinnene med effekt under PNE i større grad rapporterte ledsagende urinlekkasje (dobbelinkontinens) sammenlignet med de uten effekt. De hadde i tillegg høyere kroppsmasse-indeks (BMI). De som opplevde smerter under PNE hadde derimot dårligere effekt. Det var ingen sammenheng mellom effekt og omfanget av lukkemuskelskaden vurdert med ultralyd. I den randomiserte studien fant vi at effekten på avføringslekkasje, urinlekkasje og livskvalitet var høysignifikant i SNM-gruppen (n=30) sammenlignet med en beskjeden reduksjon i Permacol®-gruppen (n=26). Forskjell i St Marks score var 8.9 (95% CI 6.1-11.7, $p<0.0001$). I den siste studien undersøkte vi 37 kvinner med dobbelinkontinens ett år etter behandling med SNM. Totalt 13 (33%) ble kurert for urinlekkasje og 23 (62%) for avføringslekkasje. I tillegg fant vi en høysignifikant bedring av både urin score (5.8, 95% CI 3.7-8.0, $p<0.001$) og St Marks inkontinens score (10.6, 95% CI 8.6-12.7, $p<0.001$).

Som konklusjon var SNM overlegen Permacol® i behandlingen av avføringslekkasje på bakgrunn av rift i lukkemuskelen i forbindelse med fødsel. Dobbelinkontinens ble vellykket behandlet med SNM i motsetning til Permacol. Effekt av SNM var ikke relatert til omfanget av lukkemuskelskaden vurdert med ultralyd.

## ABBREVIATIONS

| | |
|---|---|
| AI | Anal incontinence |
| BMI | Body mass index |
| CI | Confidence interval |
| CONSORT | Consolidated Standards of Reporting Trials |
| DI | Double incontinence |
| EAS | External anal sphincter |
| EAUS | Endoanal ultrasonography |
| ENS | Enteric nervous system |
| EPG | External pulse generator (Verify) |
| EQ-5D™-3L | The Euroqual 5- dimension 3-level |
| FI | Faecal incontinence |
| FIQL | Faecal incontinence quality of life scale |
| IAS | Internal anal sphincter |
| ICIQ-UI-SF | International Consultation on Incontinence Questionnaire for Urinary Incontinence- Short Form |
| ICS | International Continence Society |
| IPG | Internal pulse generator (Interstim 2) |
| IQR | Interquartile range |
| OASIS | Obstetric Anal Sphincter Injuries |
| PNE | Percutaneous Nerve Evaluation |
| PRM | Puborectalis muscles |
| QoL | Quality of life |
| RAIR | The rectoanal inhibititory reflex |
| RCT | Randomized controlled trial |
| SD | Standard deviation |
| SNM | Sacral Neuromodulation |
| UI | Urinary Incontinence |
| UNN | University Hospital of North Norway |
| 2D | Two-dimensional |
| 3D | Three-dimensional |

# INTRODUCTION

The father of science, Aristotle, was born in 384 BC. His mother Phaestis died young and his father Nicomachus, who was the personal physician to the king Amyntas III of Macedonia, raised him. Medical skills were kept secret and handed from father to son. Nicomachus died when Aristotle was only 10 years old and for that reason he could not succeed his father. Instead, he became a student at Plato´s Academy. Contrary to his teacher Plato, Aristotle claimed that theories had to be modified or discarded based on observations and facts. Aristotle's theories thus constitute the origins of modern science and scientific method [1].

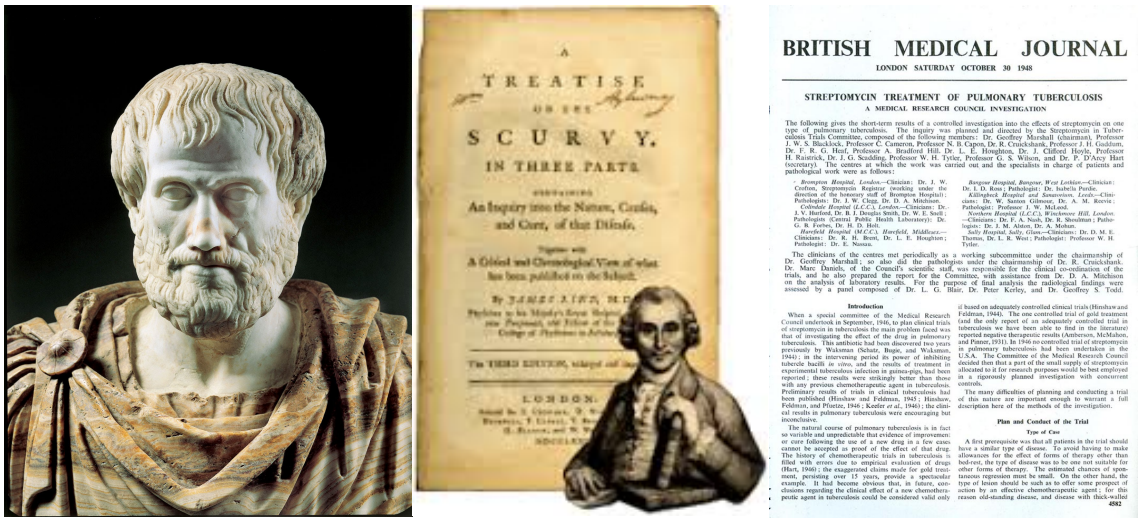



***Figure 1*** *The father of science, Aristotle (384-323 BC). The first clinical trial was published in 1747 and the first RCT in 1948*

The first clinical study we are aware of was conducted in 1747 after the Scottish physician James Lind (1716-1794) hypothesized that citrus fruits could cure scurvy. He divided 12 men suffering from scurvy at a ship into six groups, adding different nutrition to their diet. Those who received citrus fruits recovered. In 1948, Sir Austin Bradford Hill published the first study with methodological elements of a randomized controlled trial (RCT), aiming to determine the effect of streptomycin on pulmonary tuberculosis[2].

Evidence- based medicine describes a systematic approach to analyse published research and was in 1996 defined as "the conscientious and judicious use of current best evidence from clinical care research in the management of individual patients"[3, 4]. RCTs are considered

the gold standard for a clinical trial and generate evidence of the highest level when correctly conducted. The CONSORT guidelines were established in 1996 to improve and standardize conduction and reporting of RCTs [5].

Although RCTs are the gold standards, RCTs have limitations related to the complexity of medicine and surgery. Each patient and operation is unique despite standardisation and strict protocols, blinding of both the patients and surgeons are challenging to accomplish and surgical procedures are skill-dependant and constantly developing [6].

These limitations are clearly demonstrated when conducting RCTs on the treatment for complex pelvic floor dysfunction affecting several pelvic compartments with a wide range of clinical problems with major impact on quality of life (QoL), including faecal incontinence (FI), urinary incontinence (UI) and sexual dysfunction[7-9]. The aetiology is multifactorial and treatment often requires multiple specialists [10]. There is lack of international consensus on definition, classification and outcome reporting[11]. The evidence base is poor and women with a recognized sphincter defect have generally been excluded from the few existing randomized trials [7, 12, 13]. Uncertainty persists as to the optimal choice of treatment strategy for FI and concomitant pelvic floor dysfunction after obstetric anal sphincter injuries (OASIS). Hence, research on the field is warranted [12-16].

# BACKGROUND

## Faecal continence

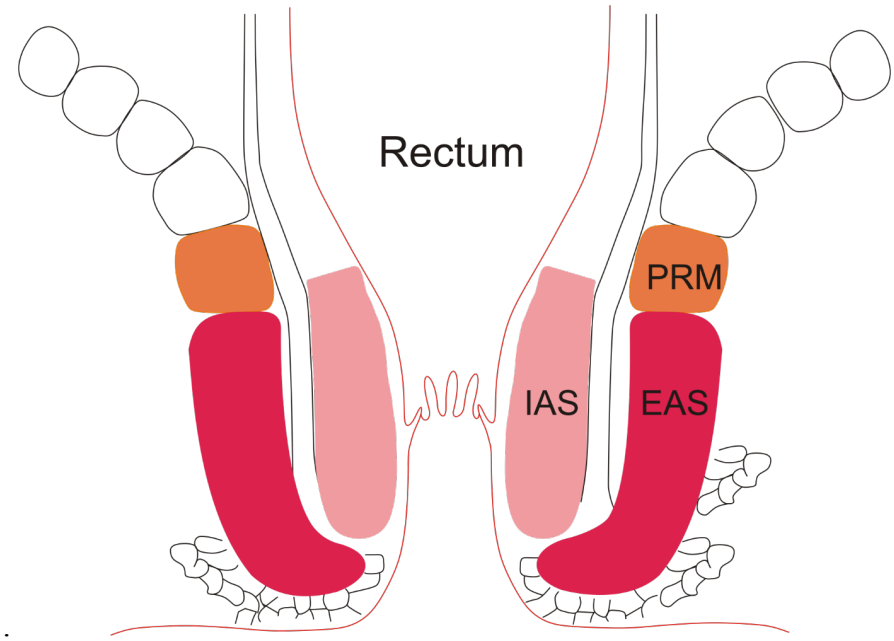
Continence is a highly complex physiological function requiring structural and neuro-hormonal integrity. Coordination of the anus, rectum, colon and pelvic floor is essential, in addition to adequate cognitive function and acquired mobility to be able to access a toilet. Factors important for continence are listed in Table 1. FI occurs if one or more of the factors are compromised [10, 17-19].

| **Structure** | **Innervation** | **Main function** |
|---|---|---|
| **Anal sphincter complex** | | |
| Internal anal sphincter | Sympatic nerves (hypogastricus)<br>Enteric nervous system | Resting anal pressure<br>Sampling reflex |
| External anal sphincter | Pudendal nerve | Voluntary squeeze pressure |
| Anal cushions | Afferent parasympathetic | Anal sensation |
| **Rectum** | Sympathetic nerves | Relaxation |
| | Parasympathetic nerves | Contraction |
| | Enteric nervous system | Sampling reflex |
| **Colon** | Sympathetic nerves | Relaxation |
| | Parasympathetic nerves | Contraction |
| | Enteric nervous system | Peristaltsis |
| **Small Intestine** | Sympathetic nerves | Relaxation |
| | Parasympathetic nerves | Contraction |
| | Enteric nervous system | Peristaltsis |
| **Pelvic floor**<br>Puborectalis muscle | Somatic sacral nerves (S2-S4) | Maintenance of anorectal angle |
| **Other** | Central nervous system<br>Peripheral nervous system | Cognitive function<br>Mobility |

***Table 1*** *Factors important for faecal continence.*

### The anorectum

The anal canal is approximately 2-4 cm long and surrounded by the anal sphincter complex involving the internal (IAS) and external anal sphincter (EAS) (Figure 2a). The IAS is a thickened extension of the circular smooth muscle of the rectum (0.3-0.5 cm). Its action is entirely involuntary, innervated by sympathetic (superior rectal and hypogastric plexus, L5) and parasympathetic nerves (nn pelvici/s2-s4) via extensions of the enteric nervous system. The main function of IAS is to maintain continence during rest. IAS accounts for 55-85% of the resting pressure, the state of contraction that keeps the anal canal closed. EAS contributes with 15-30% to the resting pressure, while another 15% is caused by anal cushions, which are connective tissue complexes containing smooth muscle cells and vascular channels [19, 20].

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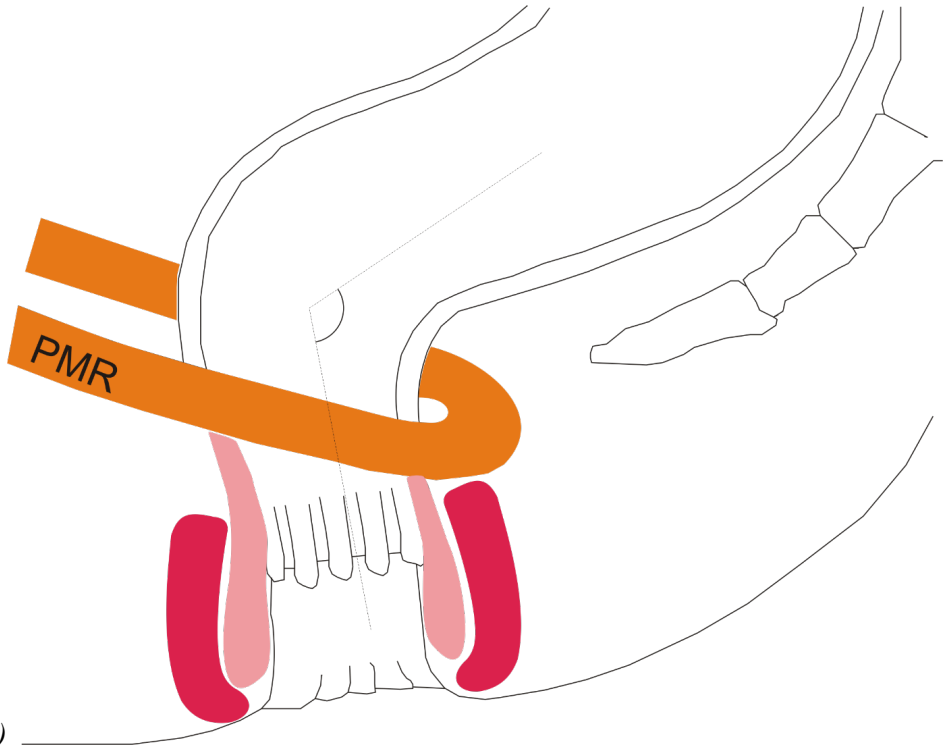
***2a)***




***2b)***

***Figure 2 a)*** *The anatomy of the anal canal with the anal sphincter complex consisting of the internal anal sphincter (IAS) and external anal sphincter (EAS)* ***b)*** *The tonic active puborectalis muscle (PRM) also contributes to continence by maintaining the anorectal angle. Illustrations by Øystein Woie.*

The EAS is striated muscle responsible for the voluntary anal squeeze. Motor and sensory nerves from the inferior rectal branch of the pudendal nerve (S2-S4) innervate the EAS. EAS continues into the levator ani, a musculotendinous sheet divided into the iliococcygeus, ischiococcygeus and pubococcygeous, which is further subdivided into the pubourethralis, pubovaginalis and puborectalis muscles (PRM), the last in close relationship to the EAS [21, 22]. The PRM is probably innervated directly by ipsilaterally branches from the sacral plexus (S3 and S4), not the pudendal nerve [18]. The tonic active PRM also contributes to continence by maintaining the anorectal angle (figure 2b) [19]. The rectum is an elastic reservoir for stool and is autonomic innervated by parasympathetic nerves from the sacral plexus S2-S4 and sympathetic branches from the mesenteric plexus, forming the rectal plexus [19]

## Defecation

The first part of defecation is involuntary and triggered by reflexes. The rectum is normally empty. Rectal distension initiates a reflectory relaxation of IAS and decrease in the resting anal pressure, the rectoanal inhibititory reflex (RAIR). This reflex is contained in the enteric nervouos system (ENS) and mediated by nitric oxid. Simultaneously EAS contracts (rectoanal contractile reflex) to augment the resting anal pressure to preserve continence. Rectal distension also increases peristaltic of colon via the intrinsic nerves (enteric ns). The sampling reflex, with transient relaxation of the IAS, allows the rectal content to interact with the sensitive epithelial lining in the upper part of the anal canal, facilitating the fine-tuning of the continence barrier by distinguishing between stool and gas[18, 19, 23].

The second part of defecation is voluntary and dependent on the desire to defecate with voluntarily relaxation of the EAS and pelvic floor muscle. The anorectal angle increases, with descent of the pelvic floor and evacuation of rectal content[19, 24]. If defecation is not socially convenient, voluntary contraction of EAS and PRM decrease the anorectal angle. The rectal content is forced back in the rectal reservoir, allowing the IAS again to contract raising the resting pressure and maintaining continence. The amplitude and duration of the RAIR increases with the volume of rectal distension. The voluntary defecation response is also regulated by the central nerves system, but the mechanism is still poorly understood [18, 19, 25]. Impaired rectal compliance can occur after radiation proctitis or inflammatory bowel disease. Hypersensitivity to distension can induce urgency at low volumes.

## Faecal incontinence

Management of FI is a neglected field within health care and surgery. The affected women suffer from physical, psychological and social disabilities[7-9].

### Epidemiology

#### *Definition*

The definition of FI is inconsistent and international consensus is lacking [18, 26]. The International Continence Society (ICS) and the International Urogynecology Association have defined FI as involuntary loss of liquid or solid stool, whereas anal incontinence (AI) has been defined as loss of faeces or flatus [27]. Urgency FI is defined as FI associated with a sudden compelling desire to defecate, difficult to defer. Passive FI is defined as FI without warning [27]. Instead of FI, the patients prefer the term accidental bowel leakage [17, 28].

#### *Prevalence*

The true prevalence of FI is not known because the subject is taboo with patients underreporting symptoms, but health professionals are also reluctant to address the subject [18, 29]. The estimated median prevalence from a recent systematic review was 7.7 % in the general adult population including both men and women older than 18 years, with increasing prevalence with increasing age [30]. The median prevalence in women was 8.9 % compared to 8.1 in men [30]. In a Norwegian survey on FI in women, 19.1% reported AI and 3.0% FI [31]. The prevalence following OASIS is estimated to 15-61%, and increasing with age [7, 8].

#### *Risk factors*

A risk factor can be defined as a factor that places the exposed at greater risk for developing the disease compared with the non-exposed. Anorectal dysfunction leading to FI is caused by a variety of conditions. More than one mechanism may contribute to development of FI and the aetiology is often multifactorial. Despite the basic understanding of FI, there are still unknown factors in the pathogenesis. Epidemiological studies on risk factors for FI are mainly based on retrospective studies [18, 23].

Common risk factors for FI include advanced age, lifestyle, colorectal and anal disorders, childbirth and OASIS, UI, systemic diseases and neurological disorders [10, 14, 23, 30, 32]. An overview of the risk factors is shown in table 2.

| **STRUCTURAL** | |
|---|---|
| Anal sphincter complex | Injury (OASIS, anorectal surgery, trauma), perianal abscess, infection and fistula, fissures, haemorrhoids, anal carcinoma |
| Rectal | Proctitis (radiation, inflammatory bowel disease), Infection, colorectal cancer, rectal prolapse or intussusception |
| Pelvic floor | Injury or trauma to muscles and nerves (OASIS, vaginal delivery) |
| Pudendal nerve | Obstetric or traumatic injuries, chronic straining, pelvic organ prolapse |
| Small intestine and Colon | GI infection, inflammatory bowel disease, colorectal cancer, food intolerance, Irritable bowel syndrome, constipation and diarrheal, malabsorption |
| **NEUROLOGICAL DISEASES** | Cerebrovascular disease, spinal cord trauma and neurological disorders such as Parkinsons disease and Multiple Sclerosis |
| **SYSTEMIC DISORDERS** | Diabetes Mellitus, sclerodermi, metabolic disorders |
| **CONGENITAL** | Anorectal anomalies (imperforate anus, rectal agenesi, cloacal agenesis), spina bifida and menigomyelocele, Hirschsprungs´ Disease |
| **FUNCTIONAL** | Age |
| | Drugs (anticholinergic, laxatives, opioids, antidepressants, caffeine, muscles relaxants) |

***Table 2*** *Risk factors for faecal incontinence. OASIS= Obstetric anal sphincter injuries*

### *Obstetric anal sphincter injuries*

Pregnancy, childbirth and OASIS are the main risk factors associated with FI in women. OASIS, classified according to Sultan et al [33], occurs in 0.5%-7.0% of vaginal deliveries. In addition, occult anal sphincter defects have been documented in approximately 30% of multiparous women[7, 33-35]. The reported prevalence of FI following OASIS is between 15% and 61% [7, 8, 10], with a twofold-increased risk of FI compared with the non-exposed [36]. Inadequate repair of OASIS and occult defects may contribute to late onset of symptoms, given the median age of symptom debut is 55 years, two to three decades after the vaginal delivery [8, 22, 23, 33, 37]. Injuries to the pudendal nerve can also occur by stretching or compression during vaginal delivery [8, 10]. The relationship between the extent of sphincter defect and clinical symptoms is, however, controversial, and the sphincter disruption is only one factor in the complexity of FI [38]. One hypothesis is that OASIS represents the “initial” of “multiple hits”[39, 40].

## Evaluation

Existing guidelines do not define when specific testing should be performed in the evaluation of FI [12, 18, 31]. Evaluation of women with FI involves a medical history aiming to identify risk factors, severity of symptoms, their impact on QoL and need for treatment. Symptom severity and disease-specific QoL can be quantified by validated questionnaires such as the St Mark’s score and the Rockwood score[41-43]. Stool consistency can be characterized by stool

scales such as the Bristol scale [44]. Physical examination and endoanal ultrasound (EAUS) is mandatory before considering surgery. Colonoscopy may be indicated to exclude colorectal pathology, while anorectal manometry is indicated in selected patients.

### *Physical Examination*

Clinical inspection and digital examination of the anal canal, rectum and vagina provides information of the thickness of the perineum and perineal body, the ano-rectovaginal septum, estimation of anal sphincter muscles thickness anteriorly in addition to resting tone and sphincter squeeze. The anal and rectal mucosa is further examined with a proctoscop.

### *Endoanal ultrasound*

The structural integrity and morphology of the anal sphincter complex can be assessed with two-dimensional (2D) and three-dimensional (3D) EAUS. Volumetric endovaginal ultrasound and transperineal ultrasound have been proposed as alternative imaging modalities to describe anal sphincter integrity [10]. Opposed to 2D EAUS, the 3D images enable visualization from different angles and enables classification of the radial and longitudinal extent of a defect, allowing differentiation between EAS and adjacent muscles and better visualization of defects[8]. Further advantages are the possibility to perform offline analysis because the images can be stored digitally and reviewed on a personal computer.[45].

Ultrasonography is based on the principles that the ultrasound waves are being reflected or transmitted when traversing the tissue (echogenicity). The reflected ultrasound waves form the images seen on the screen. Structures are characterized as hyperechoic (white on the screen, brighter) or hypoechoic (gray on the screen, darker). The IAS is hypoechoic and easily identified, and becomes thicker with age. Defects of the IAS are recognized as discontinuation of the hypoechoic ring. The EAS and striated muscles have a hyperechoic or mixed echogenicity and can be more difficult to separate from adjacent structures. The EAS in women forms an incomplete ring in the upper one third of the anal canal at the 12-o´clock position, and this finding must not be interpreted as a defect[45]. The EAS volume decreases with age. Muscular fibres are replaced with granulation tissue and fibrosis after injuries to the EAS, and defects typically present as hypoechoic areas [8, 21, 46].

The relationship between a sphincter defect on EAUS and the severity of FI is uncertain [45, 47]. Nevertheless, it has been confirmed by histology that EAS defects revealed at EAUS in

patients with FI represent true defects, implying that EAUS is important in the assessment of FI [48]. Because of the limitations related to interpretation of EAUS, a Cochrane review recommends caution when considering exclusion from trials based on EAUS defects [14].

### *Anorectal physiological testing*

Anorectal physiological testing complements examination and structural information from EAUS in the evaluation of FI includes anal manometry, anal and rectal sensation, compliance, testing of reflexes and pudendal nerve terminal motor latency-test (PNTML). Although frequently used in research, anorectal physiological testing has many limitations with a wide range of normal values and poor correlation to severity of symptoms or change after treatment. Evaluation with anorectal physiological testing was not included in the studies, because it previously has failed to provide clinically useful information in the treatment of FI with SNM or bulking injectables [8, 10, 14, 16, 38, 45, 49-51].

### *Anal manometry*

Anal manometry describes the pressure of the anal sphincter complex during rest and changes in the anal pressure during voluntary squeeze [52]. The resting pressure describes the state of contraction that keeps the anal canal closed at rest, and predominantly represents IAS function. Maximal resting anal pressure (RAP) is defined as the difference between intrarectal pressure and the highest recorded anal sphincter pressure at rest. The voluntary squeeze pressure primarily represents EAS function. Maximum Anal Pressure is defined as the difference between the intrarectal pressure and the highest pressure that is recorded at any level within the anal canal during the squeeze. Functional anal canal length is defined as the length over which resting pressure exceeds the rectum pressure[25] . IAS insufficiency is characterized by lower resting pressure whereas EAS insufficiency typically is associated with lower squeeze pressure [25, 52, 53].

### *Rectal sensation and compliance*

Rectal sensation test is performed by distending a balloon in the rectum. The lowest volume that evokes sensation (rectal sensory threshold), the volume that evokes the urge to defecate and the maximum tolerable volume with sensation of pain are measured. The rectal compliance is the relationship between change in intrarectal pressure during volume

distension and reflects rectal capacity and distensability [25]. Rectal hypersensitivity can be related to urgency and EAS defects[33].

### *Anorectal Reflex Activity*

A rapid distension of the rectum induces a transient increase in rectal pressure, followed by transient increase in anal pressure associated with EAS contraction (the rectoanal contractile reflex) and a prolonged reduction in anal pressure due to a relaxation of the internal anal sphincter (RAIR). The reflex (RAIR) indicates a normal nervous interaction between the rectum and the anal canal. The reflex is absent in patients with Hirschsprung's disease[25].

### *Pudendal nerve terminal motor latency-test*

Pudendal nerve terminal motor latency-test (PNTML) evaluates the time from stimulation of the pudendal nerve at the ischial spine to a recordable muscle contraction in the levator ani/ EAS. A prolonged PNTML-test indicates pudendal neuropathy. The test has poor intra- and inter-observer reproducibility and evaluates a compound muscle action potential, not only EAS. Consequently, the relevance of the test is controversial [8, 54].

## Treatment

The aim of any treatment of FI should be to restore continence and improve QoL. The main approaches are currently conservative management, neuromodulation and reconstructive surgery including implants and prosthesis that augment the sphincter function, and finally the creation of a stoma. So far, reconstructive surgery has not been shown to provide consistent, long-term effectiveness without complications[14, 38, 50]. If conservative treatment fails, sacral neuromodulation (SNM) is considered first line treatment, followed by individual evaluation and patients' preferences. However, international guidelines are inconsistent regarding the role of SNM versus secondary sphincter repair if the anal sphincter complex is disrupted [31, 55].

### *Conservative treatment*

Conservative management includes use of diet with fibre supplements and medication to regulate stool consistency and frequency, which affects severity of FI. Loperamide

(Imodium®) is a synthetic opioid that increases the transit time and the anal sphincter resting tone and improves rectal sensitivity. Loperamid has been shown to reduce urgency and FI episodes [56].

Pelvic floor muscle exercises including biofeedback are thought to improve FI symptoms by augmenting sensation and contraction of the pelvic floor muscles. Treatment with biofeedback is performed with an EMG probe inserted into the anorectum, providing feedback to the user during the squeeze. The effectiveness of both biofeedback and pelvic floor exercises is however controversial. No studies have reported significant differences of biofeedback or pelvic muscle exercises compared to other conservative treatments for FI. It has been believed that biofeedback and pelvic floor exercises improve rectal sensation, but the evidence are lacking [57, 58].

Patients can also be taught behavioural techniques such as scheduled toileting, use of supportive devices like absorbent padding and plugs [59], and assisted bowel evacuation such as enema and transanal irrigation [60].

### *Sacral neuromodulation*

SNM was first described in 1995 by Matzel, proposing the idea that low-voltage electrical stimulation of the sacral spinal nerves had the potential to recruit residual function of pelvic organs and modify the complex neuromuscular function required for defecation [61, 62]. SNM involves stimulation of the sacral nerve roots (S3 or S4) by an quadripolar electrode lead system connected to an subcutaneous implanted pulse generator (IPG, InterStim® Therapy, Medtronic, Inc., Minneapolis, US, Figure 3) [38].

One advantage of SNM is the staged procedure in which patients with a successful percutaneous nerve evaluation (PNE) are selected for permanent implantation, allowing the patient to test the treatment before definitive implantation of the permanent IPG. Substantial improvement during PNE predicts a successful long-term outcome of SNM [63-65]. The success-rates of SNM evaluated by a per protocol analysis in the mid- and long-term have been shown to be 80% based on a greater than 50% reduction in FI episodes, but only 60% when analysed using intention-to-treat principles [50].


***Figure 3*** *Sacral neuromodulation involves placement of an quadripolar electrode lead system in the S3 or S4 root, which is connected to an internal pulse generator (IPG, InterStim® Therapy, Medtronic, Inc., Minneapolis, US) in the subcutaneous fat of the buttock[38]."Reproduced with permission of Medtronic, Inc."*

### *Injectable bulking agents*

The concept of injection of bulking agents is to produce a bulk in the submucosa or in the intersphincteric space to close the anal canal by enhancing the anal cushions, thereby preventing FI [51]. There is no consensus on material, volume or location where the agent should be placed, with expanding indications[66, 67]. Bulking agents has been shown to improve FI in several series and randomized trials[67-70], but the clinical implication of the treatment has been questioned [51].

### *Other surgical treatment for FI*

Secondary sphincter repair is still indicated if investigation reveals a large defect or a cloacae, but the number of procedures has decreased with implementation of SNM and the deterioration of function 10 years after surgery [14]. For other surgical procedures like the artificial bowel sphincters and electro-stimulated graciloplasty, a Cochrane review concluded that it is uncertain whether surgical intervention does more good than non-surgical treatment [14]. Other innovative and promising treatments are the Gatekeeper™, the Sphinkeeper™ [71, 72] and the magnetic sphincter prosthesis [73, 74]. Ultimately a permanent stoma may be the right treatment and can improve QoL for selected patients [10, 75].

## Faecal incontinence with concomitant pelvic floor dysfunction

FI occurs rarely as an isolated pelvic floor dysfunction in women. Pelvic floor dysfunction consists of a wide range of clinical problems including UI, sexual dysfunction, pelvic organ prolapse and chronic pelvic pain in addition to FI [7-9]. FI with concomitant UI, referred to as double incontinence (DI) is reported in 30-50 % depending on the population studied [76, 77]. Female sexual dysfunction is probably present in more than 30 % [7, 77, 78]. FI, UI and sexual dysfunction are all distressing health problems leading to physical, psychological, and social disability [7-9, 79].

Vaginal birth is the main risk factor for pelvic floor dysfunctions and traumatic vaginal delivery contribute to complex damage to the pelvic floor with stretching of the pelvic floor muscles, endopelvic fascia and nerves [22]. Similar to FI, the aetiology is multifactorial and associated with OASIS and ageing with progressive neuropathy, lack of fascial support, hormonal changes and functional limitations [10, 22, 32, 80]. For DI in particular, depression and neurological diseases has been identified as risk factors [81]. The association between depression and pelvic floor dysfunction could be explained as a consequence of the disease-burden, but a dysfunction in neurotransmitters has also been suggested to contribute to DI [81]. The presence of crossed reflexes between the bladder, urethra and anorectum could explain some of the association between UI and FI [82]. Since SNM has the potential to restore both urinary and faecal continence by modification of nerve activity, SNM has been suggested as a viable treatment option for DI if conservative treatment fails [12, 62].

The complex nature of pelvic floor dysfunctions may require assessment by multiple specialists such as surgeons, uro-gynaecologists, urologists, radiologists, specialist nurses, physiotherapists and psychologists. As a consequence, pelvic floor units have emerged internationally.

## AIMS OF THE STUDY

The overall aim of the PhD thesis was to investigate SNM and injection of bulking with Permacol® for FI and concomitant pelvic floor dysfunction in women with a history of OASIS.

Some clinical questions and observations formed the basis for the hypotheses and design of the study protocol in 2011. The **first** question was whether the effectiveness of Permacol® was comparable to SNM in women with FI following OASIS. The use of bulking agents became widespread due to their simplicity and suggested cost-effectiveness compared with SNM [83]. SNM and injection of bulking agents had not been compared in a randomized controlled trial, and uncertainty persisted about the optimal choice of treatment for postobstetrical FI, and a comparison between the two minimally invasive treatments was warranted [12-16]. The comparison between the two treatments was presented in paper II.

The **second** question was whether the effectiveness of SNM or bulking injectables for FI following OASIS was related to the extent of the pre-existing sphincter defect. Both the European bowel study group [84] and a review [85] emphasized the poor quality of the few published studies and the need for well-designed prospective studies. The correlation between effectiveness and extent of the sphincter defect was analysed in paper I-III.

The systematic use of questionnaires for assessment of pelvic floor dysfunction in the pelvic floor unit revealed a high prevalence of concomitant UI. The **third** question was whether concomitant UI and pelvic floor dysfunction was treated effectively with SNM. This question was addressed in paper I-III.

***Aim paper I***

The purpose of the first study was to assess efficacy during the three-week PNE using the tined lead and the Verify® external pulse generator (EPG) in patients with FI and a history of OASIS. Outcome was related to baseline factors with special emphasis on the extent of sphincter defect.

***Aim paper II***

The purpose of the second trial was to compare the effectiveness of SNM with injection of bulking with collagen (Permacol®) in women with FI following OASIS.

***Aim paper III***

The purpose of the third study was to investigate the effectiveness of SNM for combined UI and FI (DI) following OASIS. Outcome was related to baseline factors.

# METHODS

## Study design

The study design included prospective collection of data in consecutive patients with FI and a history of OASIS. Figure 4 illustrates the study design from assessment of eligibility to 12 months follow up and paper I-III related to the entire study population. The study was managed from the tertiary colorectal referral unit at the University Hospital of North Norway (UNN).

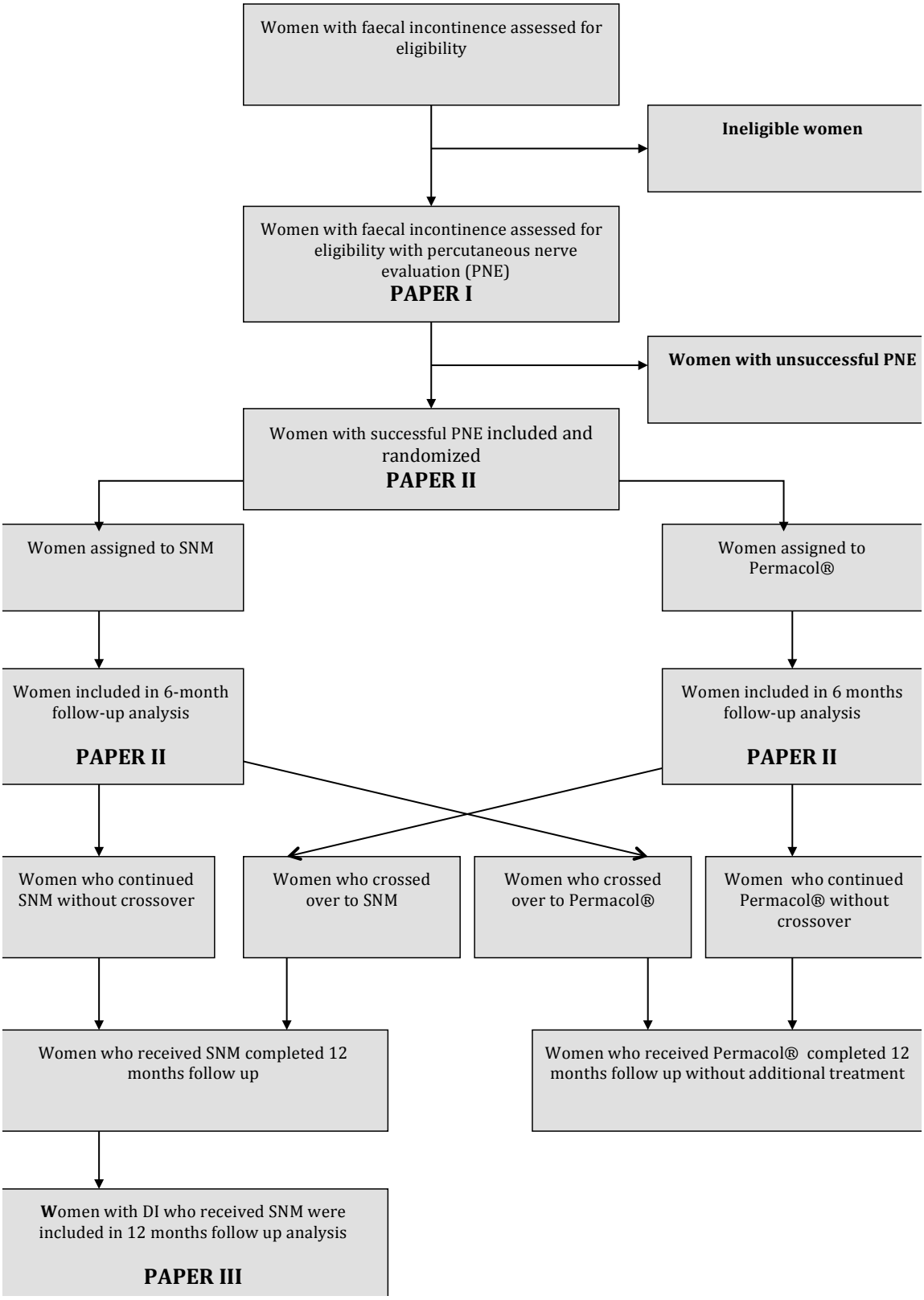



***Figure 4*** *Flow chart illustrating the study design and the three papers in relation to the study-population*

## Inclusion and exclusion criteria

All the papers involved women with severe FI following OASIS, representing the largest subgroup of patients with FI [14]. The patients were recruited from the outpatient clinic at the tertiary colorectal referral centre at UNN and St Olavs hospital, Trondheim, after failure of conservative treatment.

Substantial FI was defined as St Mark's incontinence score of more than 8, and weekly FI episodes of loose or solid stool despite optimal conservative management. An international consensus and a clear definition of severe FI and successful treatment of FI is lacking[11]. A weekly FI episode is a common applied inclusion criterion for SNM[49], with 50 % reduction of weekly FI episodes as definition of success, but has been criticized as a outcome measure for treatment for FI[11]. The St Mark's score has been shown to correlate to QoL in women with a history of OASIS [86] and a score grater than 8 has been shown to be associated with deteriorated QoL [87]. Therefore, a cut of value of 8 of the St Mark's score in addition to weekly FI episodes was used as the definition of severe FI.

Conservative treatment included at least 6 months tailored management with supportive devices, including paddings and plugs, dietary modification, constipating medication, pelvic floor exercises with or without biofeedback and trans-anal irrigation. Tailored conservative treatment was initiated at the outpatient clinic and monitored by specialized nurses affiliated at the National Advisory Board of Continence and Pelvic Floor Health of Norway, UNN.

OASIS was defined as a third- or fourth-degree perineal tear during childbirth [35]. Because the women were referred from hospitals throughout Norway, information regarding the OASIS and primary repair was incomplete. Women with FI and a history of OASIS were eligible for inclusion regardless whether a sphincter defect was revealed at EAUS or not. No upper limits of the extent of sphincter defects were defined. All eligible women were considered for enrolment in the trial and not for secondary sphincter repair. The exception was the presence of a cloaca, which would require reconstructive surgery for other reasons than primarily treatment of FI. The inclusion and exclusion criteria are listed in Table 3.

| Inclusion criteria | Exclusion criteria |
|---|---|
| History of OASIS | Pregnancy |
| Faecal incontinence with St. Mark's score > 8 and weekly incontinence episodes | Immunosuppression |
| Failed **conservative treatment** (dietary modification or constipating medication, pelvic floor exercises with or without biofeedback, supportive devices such as pads, plugs, and trans anal irrigation) | Previous major pelvic surgery including irradiation to pelvic organs for cancer within the past five years |
| Informed consent | Untreated rectal external prolapse |
| 18 years or older | Untreated perianal fistula |
| | Active Inflammatory Bowel Disease (IBD) |

***Table 3*** *Eligibility criteria*

### *Inclusion and exclusion criteria paper I*

This study included all the women with FI following OASIS enrolled at UNN who underwent a three-week PNE. The patients from St Olav Hospital were excluded because the 3D EAUS datasets were unavailable.

### *Inclusion and exclusion criteria paper II*

The women with FI and a history of OASIS who had a successful PNE were randomized, because a successful PNE is a prerequisite for definitive implantation of an IPG [55]. Patients were recruited from both St Olav Hospital and UNN.

### *Inclusion and exclusion criteria paper III*

The third study included the women with combined UI and FI that received SNM. In addition to the eligible women randomly allocated to SNM, the women primarily assigned to Permacol® and who crossed over to SNM after 6 months, were included (Figure 1). UI was defined as concomitant if ICIQ-UI-SF score was one or greater. Women with isolated FI and those who discontinued treatment with SNM before 12 months follow-up were consequently excluded.

## Procedures

### Sacral neuromodulation (SNM)

All the patients were invited to participate in group-conversations the day before surgery with 6 to 8 patients according to hospital practice. An experienced nurse led the group-conversations and the surgeons were available for answering questions. Information about the treatment and the postoperative period were given and the patients had the opportunity to share experiences and questions.

The PNE procedure was performed with local anaesthetic in combination with monitored sedation. Intravenously antibiotic prophylaxis with Cefuroxim was administrated preoperative. The same team with one surgeon performed all procedures. The surgical procedure was standardized using a tined lead and the *straight* stylet (3093, Medtronic, Minneapolis, Minnesota, USA). The tined lead was placed through the S3 or S4 foramina using Seldinger's technique and fluoroscopy. According to recommendations [88], the tined lead was positioned to achieve a low-threshold motor response on as many of the four electrodes as possible. The tined lead was connected to an EPG (Verify® model 3531, Medtronic) by an extension wire. Three programs eliciting a low-threshold sensory response, with best response defined as sensation nearest to the anus, were established in the operating room. The EPG was turned on and the response controlled after the patients had recovered from the anaesthesia.

Patients were discharged after learning to adjust stimulation with the patient controller (Model 3537, Medtronic). Participants were offered sick leave for the entire 3-week PNE period and were followed by weekly phone calls according to hospital routine. Instructions for readjustment, including change of amplitude, were repeated to patients who reported suboptimal response or painful stimulation.

The extension wire was cut at skin level by the general practitioner after three weeks, terminating the PNE period. Cutting the extension wire at skin level after the PNE period has been a part of the routines since the tined lead was introduced to the standard PNE procedure as an alternative to the temporary lead in 2008. In patients who had a successful PNE, the tined lead was left in place for definitive implantation, usually two to four weeks after terminating the PNE. For women assigned to SNM, the tined lead was connected to an IPG (Interstim II 3058 Medtronic, Minneapolis, MN, USA) and placed in a subcutaneous pocket

(Figure 5). The procedure was performed in local anaesthesia in combination with monitored sedation. Intravenously antibiotic prophylaxis with Cefuroxim was administrated preoperative in combination with an implant impregnated with gentamicin (Collatamp®). The same procedure was performed in the women who were primarily assigned to injection of Permacol®, but crossed over to receiving delayed implantation of SNM after 6 months follow As for the EPG, the IPG was programmed to elicit a low-threshold perianal sensory response.

All of the patients received a patient programmer (ICon® 3037, Medtronic, Minneapolis, MN, USA) allowing adjustments or turning the stimulation on and off. The IPG was reprogrammed at the prescheduled follow-ups at 3 and 6 months in case of adverse events such as painful stimulation, deterioration of urinary function or persisting weekly FI episodes. A specialized nurse (WJ) was available to answer questions by telephone between the prescheduled follow-ups.

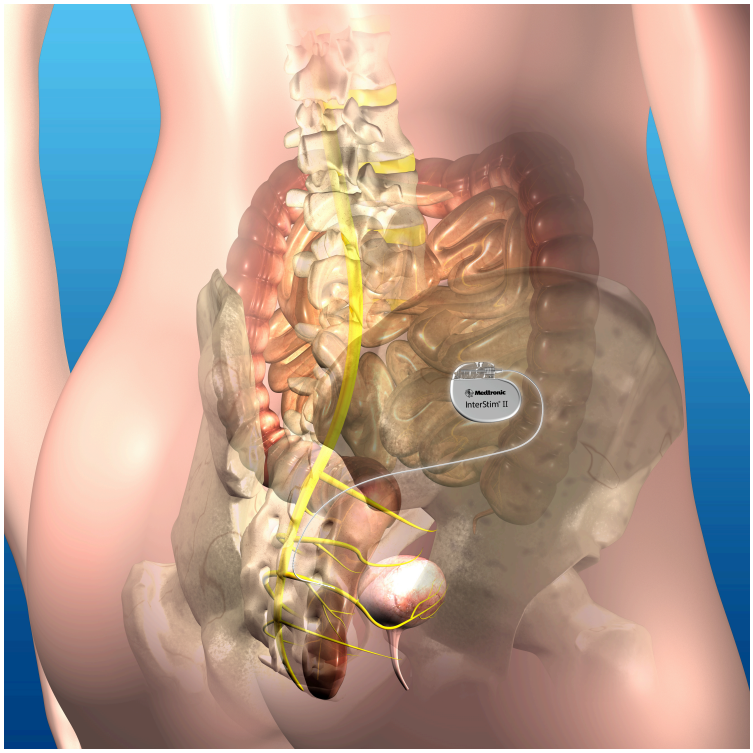



***Figure 5*** *InterStim II is an implantable, programmable medical device that deliver electrical stimulation to sacral nerves. "Reproduced with permission of Medtronic, Inc."*

### Injection of bulking agent with collagen (Permacol®)

Cross-linked porcine dermal collagen, Permacol® (Tissue Science Laboratories, Aldershot, Hampshire, UK) was used as a bulking agent. The procedure was performed at the outpatient clinic, without anaesthesia or bowel preparation. Antibiotic prophylaxis (Ciprofloxacin 500 mg x2) was given orally. Two surgeons performed all the procedure (MR, TD). The Permacol® injectable bulking agent was delivered in two attached syringes, one empty and one prefilled containing Permacol®. By passing the solution back and forth between the two syringes about 20 times, an adequate mixture for injection was achieved. In the lithotomy position, 1.5 mL Permacol® was injected via a proctoscope into the sub-mucosa to produce a bulge just above the dentate line in each of the four quadrants[66, 68, 69]. The needle was retained in the injection tract for about 5 seconds to prevent the leakage of the bulking agent (Figure 6). The procedure was repeated after three months in case of weekly FI episodes and in the absence of adverse events. For women allocated to Permacol®, the tined lead was left in place until 6 months' follow-up. Crossover with delayed implantation of the IPG was offered in the case of an inadequate response to Permacol® at six months follow-up.

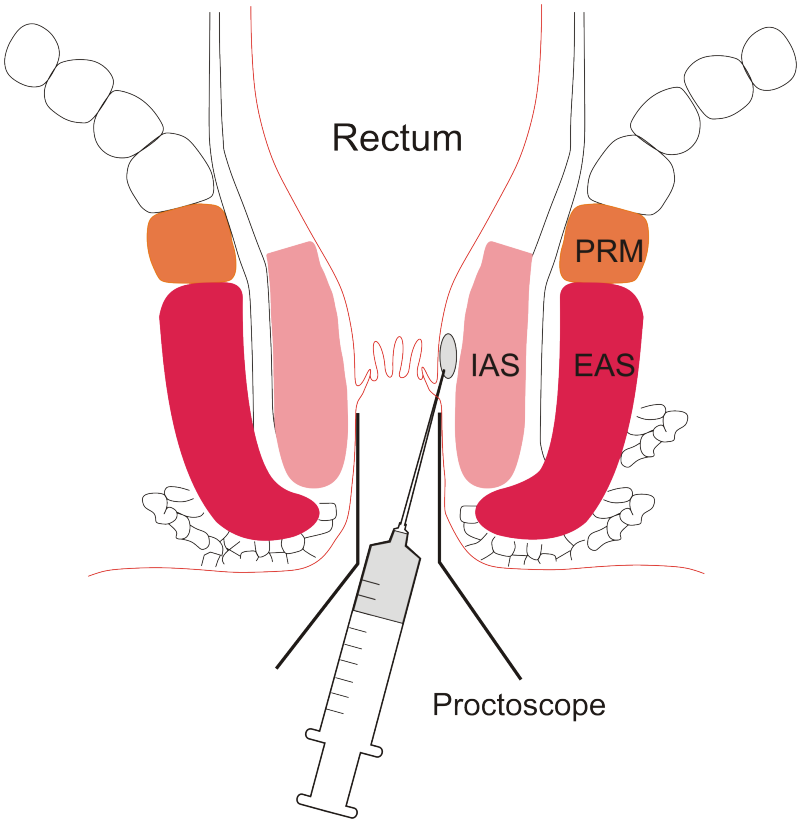



***Figure 6*** *Submucosal injection of bulking with collagen (Permacol®) via proctoscope. IAS= internal anal sphincter, EAS=external anal sphincter, PRM= puborectalis muscle. Illustration by Øystein Woie.*

Permacol® was selected as bulking agent in this trial because the efficacy of an alternative compound (dextranomer in stabilized hyaluronic acid, NASHA Dx) was disappointing with no differences compared to traditional biofeedback [66]. Symptom scores and the QoL were also unchanged in a multicentre RCT comparing NASHA Dx with placebo [68]. On the other hand, Permacol® was believed to be incorporated into the tissue, resist breakdown by collagenase, and thereby maintain a long-standing bulk in the submucosa [69].

## Evaluation

Baseline evaluations included civil and work status, body mass index (BMI), medical and obstetric history. Anorectal examination and EAUS was performed in all the women. Patients were also asked to complete a two-week bowel habit diary and the questionnaires[41, 42, 79, 89] used for outcome assessment. Although commonly applied as outcome measures for PNE, scoring systems such as the St. Mark's score[41] and Rockwood QoL[42] are not designed or validated for measuring changes over a short intervals such as the three-week PNE period. Consequently, evaluation of PNE was based strictly on change of weekly FI episodes assessed with bowel habit diaries [50, 84].

Outcome assessments of St Mark's score, ICIQ-UI-SF and sexual function were performed blinded by telephone interview prior to the prescheduled follow-ups at baseline, 3 months, 6 months and 12 months follow up.. The two-week bowel diary and QoL questionnaires were mailed for self-reporting. Self-reported outcome assessment (satisfied/not satisfied) was evaluated at 6 months follow up. Adverse events such as infection, pain or adverse changes in bowel or urinary function, were recorded during the follow-up consultation, not by telephone, because this could have revealed the treatment arm. An overview of the evaluation at different time points is given in Table 4. Optical readable forms were used for all templates and questionnaires (appendix).

| Baseline | PNE | 3,6 and 12 months follow-up |
|---|---|---|
| **Demographic data:**<br>Age (years)<br>Menopausal status<br>Body mass index (BMI, kg/m$^2$)<br>Obstetric history<br>Previous surgical procedures<br>3D EAUS defect score [46] | | |
| **Questionnaires**<br>St. Mark's incontinence score [41]<br>FI QoL score (Rockwood FIQL)[42]<br>EQ-5D™ (EuroQol Group, Rotterdam, the Netherlands)<br>UI (ICIQ-UI SF) [89]<br>Sexual function [79] | | **Questionnaires**<br>St. Mark's incontinence score<br>FIQL score<br>EQ-5D™<br>ICIQ-UI SF<br>Sexual function<br>6 months: Patients satisfaction |
| **2-week bowel habit diary:**<br>Weekly FI episodes<br>Weekly urgency episodes<br>Weekly bowel-emptying episodes | **3-week bowel habit diary:**<br>Change in weekly FI episodes, urgency episodes, bowel-emptying episodes | **2-week bowel habit diary:**<br>Change in weekly FI episodes, urgency episodes, bowel-emptying episodes |
| **Procedure** | Sensory threshold<br>Foramen (level)<br>Adverse event | Sensory threshold<br>Adverse event |

***Table 4*** *Evaluation at baseline, after PNE and later follow-ups (3, 6, 12 months***)**

## Sphincter defects

The sphincter complex was examined with 3D EAUS with the patient in the lithotomy position at the time of inclusion. A Falcon ultrasound scanner was used (BK medical, Gentofte, Denmark). The 3D film of the anal sphincter complex was recorded from the distal part of the PRM to the anal opening by continuous motorized withdrawal. The 3D EAUS dataset was stored on a personal computer. The extent of the defect was classified according to the validated EAUS defect score [45, 46]. Classification was performed using the BK 3D viewer by an independent investigator (SN) blinded to clinical data.

The EAUS defect score ranges from 0 (no defect) to seven (maximal defect with defect in both external and internal anal sphincter) (Table 5). Partial defects of IAS were excluded. Defects being complete at one level and partial at another level were defined as complete in the whole extent of the defect.

| *Defect characteristics* | *Score 0* | *Score 1* | *Score 2* | *Score 3* |
|---|---|---|---|---|
| ***External anal sphincter*** | | | | |
| *Length of the defect* | *≤50%* | *>50%* | | |
| *Depth of the sphincter* | *None* | *Partial (≥50%)* | *Total and ≤90˚ radial extension* | *Total and >90˚ radial extension* |
| ***Internal anal sphincter*** | | | | |
| *Length of the defect* | *≤50%* | *>50%* | | |
| *Depth of the sphincter* | *None* | *Total and ≤90˚ radial extension* | *Total and >90˚ radial extension* | |

***Table 5*** *The EAUS defect score. The score is continuous and ranges from 0 to 7. The EAUS defect score is calculated by summarizing the value given from the different parameters, from external (maximum 4) and inter anal sphincter defect (maximum 3) [46].*

Different classification systems are used to describe the extent of the sphincter defects. Both the EAUS defect score and the Starck score have been shown to correlate with the degree of FI following OASIS [90-92]. The EAUS defect score is the preferred classification system in our practice, because it has a continuous scale and do not classify partial defects of the IAS in contrast to the Starck's score [46, 92].

### St Mark's score

St Mark's incontinence score is an interview scoring system used to grade the severity of FI during the last four weeks. St Mark's score consist of seven question and range from 0 (no FI) to 24 (maximal FI)[41]. Difference in the reduction of St Mark's score from baseline to six months was the primary outcome measure in paper II.

### Bowel habit diary

Patients completed a two -week bowel habit diary at baseline recording weekly FI episodes, differencing between urgency and passive FI episodes. Urgency was defined as inability to defer defecation for 15 minutes. In paper I, the bowel habit diary was used to assess primary outcome expressed as per cent reduction in weekly FI episodes, with a successful PNE defined as a 50% or greater reduction of weekly FI episodes.

### Faecal incontinence quality of life scale

The rockwood FIQL scale is a disease specific health related QoL questionnaire that has been translated and validated into Norwegian[42, 43]. FIQL is composed of 29 items based on self-

report, rating from 0 (worst) to 4 (best). The items are dived into four subscales, which are the mean of all the items included in the respective scale: Lifestyle (10 items), Coping (9 items), depression (7 items) and embarrassment (3 items).

### EQ-5D- 3L

The Euroqual 5- dimension 3-level (EQ-5D™-3L) is a commonly used generic QoL questionnaire that consists of five question assessing mobility, self-care, daily activities, pain and depression with 3 possible answers. The sum of the answers can be converted into the EQ-5D index that ranges from -0.543 (worst) to 1.0 (best). A score less than 0 indicate QoL worse than death. In addition, a visual analogue scale (VAS) from 0 (worst) to 100 (best) is used to describe the patients' self-perceived general health status. Normative data for the Norwegian population are not available [93, 94].

### ICIQ-UI-SF

All women were screened for concomitant UI with the validated International Consultation on Incontinence Questionnaire for UI, Short Form (ICIQ-UI-SF)[89]. The ICIQ-UI-SF is constructed to measure both level of symptoms of UI and impact on lifestyle the last four weeks, and consist of three numeric questions and seven self-diagnostic items defining stress and urge UI. The ICIQ-UI SF ranges from 0 (no UI) to 21 (worst UI) and is graded from mild (1-5), moderate (6-12), severe (13-18) to very severe (19-21). UI was defined as concomitant if ICIQ-UI-SF score was one or greater[89]. Change in ICIQ-UI-SF from baseline to 12 months was the primary outcome in the paper III.

### Sexual function

Sexual function was assessed by a translated non-validated questionnaire designed for women with OASIS, developed by an expert group [79]. The questionnaire is easy to use, can be applied for telephone interview and contains the following four questions: 1. Are you sexually active? (Yes/no) If no, state reason. 2. Is sex painful? (Yes/no) 3. Do you have any problems with sex? (Yes/no) If yes, state problem. 4. Are any of your sexual problems bothersome? (Yes/no). The expert group highlights the importance of assessment of bothersome sexual problems to avoid over-diagnosis of sexual complaints [79].

## Primary and secondary outcome

***Paper I***

The purpose of paper I was to assess efficacy during PNE and relate the outcomes to baseline factors with special emphasis on the extent of sphincter defect in women with FI following OASIS. The primary outcome was efficacy defined as the per cent reduction in weekly FI episodes during PNE compared with baseline and the success rate of the PNE, with a successful PNE defined as a 50% or greater reduction in FI episodes.

***Paper II***

The purpose of paper II was to compare the effectiveness of SNM with Permacol® in women with FI following OASIS. The primary outcome was the difference in the St. Mark's score between baseline and 6 months. Secondary outcomes were changes in weekly FI episodes, disease-specific QoL (FIQL), generic QoL (EQ-5D), UI (ICIQ-UI-SF) and sexual function.

***Paper III***

The purpose of paper III was to investigate the efficacy of SNM in women with a history of OASIS and combined UI and FI. The primary outcome was the change in ICIQ-UI-SF at 12 months compared with baseline. Secondary outcomes included reduction of St Mark's score, change in QoL scores and sexual function.

## Sample size calculation

The sample size calculation was based on the power calculation from the RCT. The assumption was that a difference greater than 4 points in the reduction of the St. Mark's score between baseline and 6 months between the SNM-group and Permacol® -group, was clinically relevant. Detecting this difference with a statistical power of 0.80 and a significance level of 0.05 with a two-sided test, and assuming a standard deviation of 5.0, would require 25 patients in each group. Accounting for a dropout rate of 10%, assignment of 28 participants in each group was considered adequate. With a success-rate of PNE of 70-90 %, a total of 62-73 women had to be enrolled and assigned to PNE. The sample size was calculated for the RCT and the studies were not powered to detect differences between or within subgroups.

## Randomization

In paper II, the participants were randomly assigned to receive either SNM or Permacol® with an equal allocation ratio (1:1), with randomly permuted block sizes of varying length (6 and 4) to conceal the allocation. Patients were stratified according to the centre of recruitment. Allocation was performed by a computer-generated, real-time, web-based randomization system (www.ntnu.no/dmf/akf/randomisering) that generated random allocation sequences known only by the administrators responsible for developing the randomization system until the study was closed. Local investigators implemented assignment to intervention.

## Blinding

Double blinding may be challenging in surgical trials. Because two different treatments were compared in this RCT, sham was not an option and blinding of patients and surgeons were not accomplished. To avoid assessment bias, the telephone interview prior to the 3- and 6-month follow-up was performed by a trained nurse (GN) who was blinded to treatment allocation throughout the study period. The patients were instructed not to reveal the treatment arm by an information letter mailed prior to the phone call. The classification of the extent of the EAUS defect was also performed blinded by an experienced investigator (SN).

## Statistical considerations

Continuous variables were presented as mean with standard deviation (SD) or medians with interquartile range (IQR). Within group differences were analysed with paired t-test. Between group differences were analysed by independent t-test and linear regression models. The effect sizes were presented as the mean with 95% confidence interval (CI) and a two-sided significance level of 0.05. Model assumptions were assessed by residual analyses. For the linear regression analyses model assumptions were assessed by graphical inspection of the residual. The residuals should be approximately normally distributed and the the variance of the residuals should not depend on values of the independent variables (homoscedasticity).

The nonparametric Mann Whitney-U test and Wilcoxon signed rank test were used when assumptions not were met. Categorical data were reported as frequencies and percentages and compared using the chi-squared test or the two-tailed Fisher's exact test. Correlations were assessed with Pearson correlation coefficients (r). Association and odds ratio (OR) were assessed with linear and logistic regression models, both unadjusted and adjusted. A two-sided P value <0.05 was considered statistically significant. All analyses were performed using the SPSS program, version 21.0-23.0 (SPSS Inc., Chicago, Illinois, USA).

Linear and logistic regression models were used to assess the associations between efficacy during PNE (paper I) or effectiveness (paper III) and baseline independent variables with special emphasis on the extent of sphincter defect. Significant variables from unadjusted regression models were included in multivariable regression models. Outcome variables in paper II were analysed using a linear regression, unadjusted and adjusted for the baseline symptom scores as covariates (ANCOVA) according to recommendations [95, 96]. ANCOVA was pre-specified as the primary analysis in the study protocol. Binary variables were presented as the number and percentage, and analysis of group differences regarding change from baseline to 6 months was assessed by a generalized estimating equation using the logit link function (Paper II).

## Additional analysis

We recognized that the study design in the RCT where a successful PNE was an inclusion criterion might have introduced a selection bias in favour of SNM, selecting patients responsive to SNM. To overcome this inherent selection bias, as recommended[50], a worst-case scenario for SNM was created as follows: Of the seven women with unsuccessful PNE who were excluded, four were allocated to the Permacol® group. Each patient was given the best reduction in St Mark's score obtained after Permacol® injections in the Permacol® group. The other three were allocated to the SNM group, each given a reduction of zero in St Mark's score (poorest possible). In this way, the best possible outcome after Permacol® injection could be compared with the worst possible outcome after SNM. The primary outcome was then analysed.

Because of imbalanced recruitment between the two centres, an additional sensitivity analysis excluding the two patients from St Olav's Hospital was performed.

### The CONSORT guidelines

The CONSORT guidelines [97] were followed to ensure high quality of reported results and avoid bias in the RCT [98]. The consort guidelines facilitate standardized and transparent reporting and interpretation and consist of a statement, checklist and flow diagram.
The CONSORT Statement is evidence-based recommendations for reporting randomized trials and comprises a 25-item checklist focusing on the design, analysis and interpretation of findings. The CONSORT flow diagram displays the progress of all participants through the trial.

## Methodological strengths

The prospective collection of data with the randomized design represents the highest level of evidence in evidence-based medicine.[4] Random allocation decreases selection bias and minimizes confounding variables when comparing the groups. Consequently, the conclusions are not due to chance if an adequate sample size has been calculated.

One of the main strengths of the study was restricting the study group to women with FI following OASIS. This group represents the largest subgroup women with FI and treatment is based on low level of evidence[12]. Consecutive women were included irrespective of the size of the sphincter defect, which were classified blinded according to a validated 3D EAUS defect score. Another strength was a multidisciplinary approach with the use of validated questionnaires for blinded assessment of FI, UI and QoL. A non-validated questionnaire for sexual function was used, because it included assessment of bothersome sexual complaints. The advantages of questionnaires are that they are easy to apply, cost effective and they allow for masked outcome assessments.

Finally, the standardization of the method including the tined lead and use of the new EPG was a strength. One advantage using a tined lead and not a temporary lead during PNE is the standardized positioning of the tined lead to achieve low motor and sensory thresholds on three to four poles. The stimulation during PNE becomes similar to permanent treatment. When achieved, low threshold stimulation is believed to improve the outcomes of both PNE

and permanent SNM[99-101]. The new EPG (Verify®) is also more stable than the previous model and enables delivery of more accurate amplitude similar to permanent stimulation.

## Methodological limitations

Preferably, an RCT should be double blinded to prevent bias and protect the randomization sequence after allocation. Lack of blinding of participants may introduce a bias and the outcome estimates may deviate from the true effect of the intervention, either as an underestimation or an overestimation. It is possible, that participants in the Permacol® group would be disappointed by the allocation to a less expensive treatment, with less expectations and motivation to report improvement compared to participants in the SNM group who might have reported an exaggerated effect. Another possibility is that patients receiving the less effective treatment would search alternative treatment. Unmasked surgeons may also have transferred their attitudes about the different treatment to the participants, both unintentionally and intentionally. This could have impacted the outcome estimates. The lack of patient blinding is consequently a limitation of the trial.

Questionnaires have limitations: The significance is primarily dependent on the reliability and the validity of the questionnaires. Secondly, questionnaires do not necessarily address the problems important for patients. Patients and health professionals may also have different view on the weighted severity of different symptoms [11, 29, 102]. The burden of FI and concomitant pelvic floor dysfunction may not be easily interpreted from the bowel habit diary, St Mark's score and other questionnaires. Likewise, the efficacy of treatment is not automatically reflected by the changes in scores. Interestingly, for EQ-5D-3L the normative data for the Norwegian population are not available. It is challenging to judge whether a difference is clinically relevant or not, making the interpretation uncertain. The lack of an international consensus in the definition, assessment and outcome-reporting for the treatment of pelvic floor dysfunction, is consequently one of the main limitations in these studies [11].

One disadvantage by many RCTs is the time used to perform a trial. While this trial was ongoing, clinical practice moved on. In light of current evidence, bulking agents as comparator to SNM may have been replaced by other treatments, like transanal irrigation, the Gatekeeper™ or the Sphinkeeper™ [38, 51, 60, 71, 72].

## Ethical consideration, trial registration and funding

The study protocol that formed the basis for application for funding and admission to the PhD program was completed in 2011. The study was funded by the medical research programme of the Health Authorities of North Norway, grant reference number ID 6916/SFP1049-12, with 50% salaries for 6 years, from 2012-2017. No commercial organizations were involved in the trial. MR has received honorarium from Medtronic for a presentation in September 2016. The other authors have no disclosures.

The study was initiated in February 2012 after The Regional Committees for Medical and Health Research Ethics, North Norway approved the protocol (number 2011/1300/REKnord). The trial was registered at ClinicalTrials.gov with number NCT01528995.

Written informed consent was obtained from all participants at baseline. The consent included completion of the PNE period, treatment with Permacol® if unsuccessful PNE and randomized allocation to either Permacol® or SNM if successful PNE. The 50 % chance of allocation to the Permacol® group despite a successful PNE was thoroughly discussed with the patients before obtaining written informed consent. In addition, the consent contained cross over to the other treatment arm after 6 months and 12 months follow up.

# RESULTS

## Study overview

Between February 2012 and March 2014, 77 consecutive women were assessed for eligibility. A total of 63 women underwent the 3 weeks PNE period at UNN and 2 women underwent a PNE period at St Olav hospital. At UNN, one woman declined to participate, three were excluded according to exclusion criteria and another eight women signed, but withdrew informed consent for various reasons. The efficacy during PNE and relation to baseline factors is discussed in paper I.

Of the 58 women with a successful PNE, 56 from UNN and two from St Olav's Hospital were randomly assigned to SNM (n=30) or injection of Permacol® (n=28). Two patients withdrew their consent before entering treatment in the Permacol®-group. Except for these two, all patients were available for analysis at six months. The comparison between the two treatment groups is presented in paper II.

Crossover from one treatment arm to the other arm was allowed after 6 months. None of the patients in the SNM group crossed over to Permacol® compared to 18 of 26 (69%) who received Permacol® that crossed-over to SNM. Three of these women were lost to follow up: One patient discontinued treatment with SNM because of infection. Another reported intolerable pain possibly related to a chronic infection, not verified by culture. The third woman died of cardiac arrest, unrelated to SNM. Consequently, a total of 45 women were available for analysis 12 months after SNM. Paper III includes the analysis of the 37 women who reported combined FI and UI (DI).

Another three patients (12%) in the Permacol® group preferred additional treatment other than SNM: A secondary sphincter repair was performed in one woman with a major defect of both EAS and IAS and with an EAUS defect score of 7. One chose transanal irrigation in combination with fibre supplements and another woman received a permanent colostomy. Finally, five women (19%) were satisfied with the result after Permacol® injection and did not request additional treatment after 6 months follow up (Figure 7).

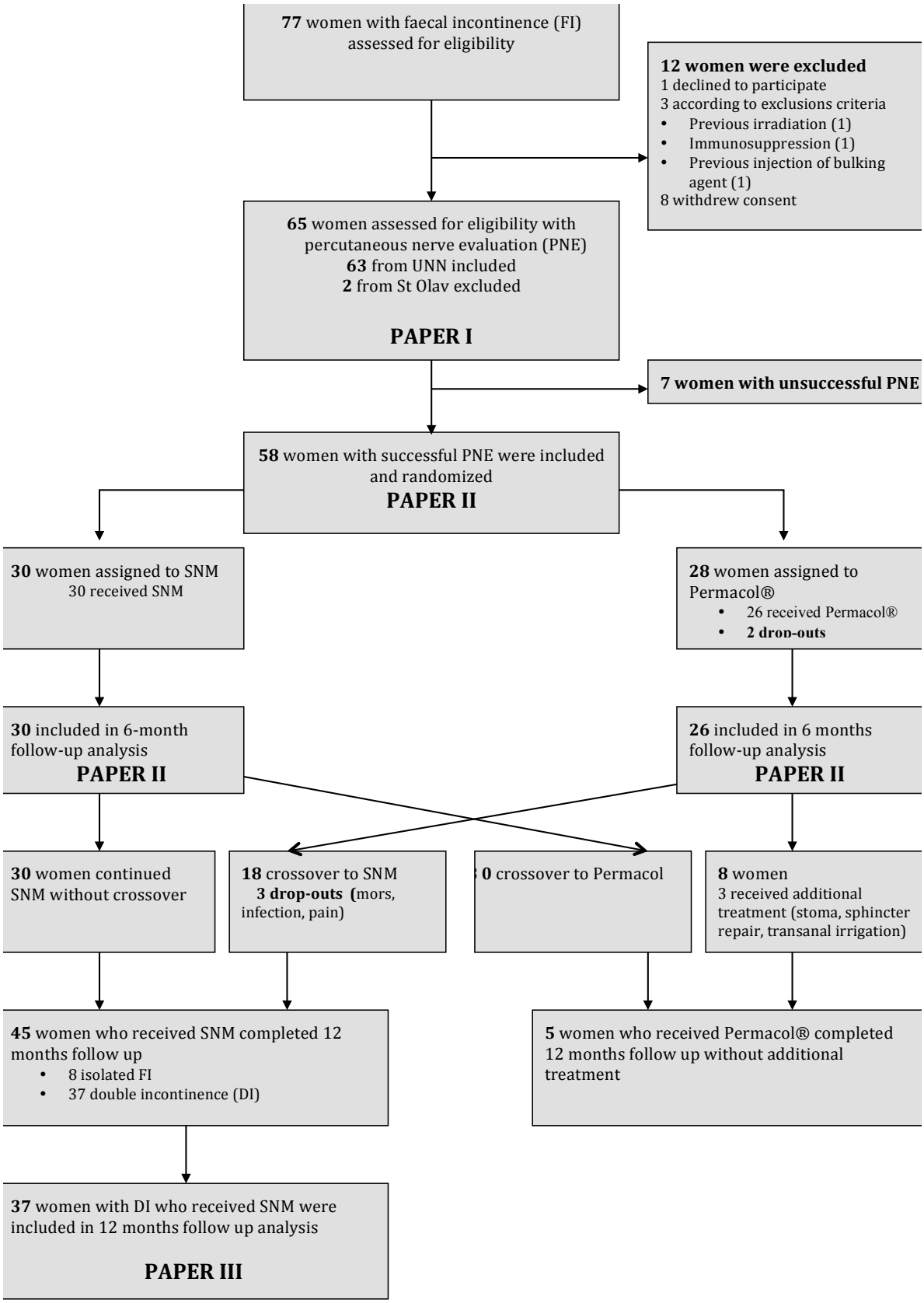



***Figure** 7 Flow chart of all the women with faecal incontinence following OASIS assessed for eligibility from baseline to 12 months follow up*

The trial was closed in September 2015 after reaching the sample size and completing 12-month follow-up examinations. In the same period, from February 2012 to March 2014, 14 men and 15 women with FI without a history of OASIS underwent PNE at UNN. Secondary sphincter repairs and perineal reconstruction were performed in four women because of the combination of cloaca, large rectoceles or lack of perineal body.

## Baseline characteristics of all the participants (n=65)

The mean age of the enrolled women were 56.5 (SD 12.5) years and 45 (69%) were postmenopausal. The mean BMI was 26 (SD 4.4). Forty-three (66%) lived with a partner. Demographic data and baseline characteristics of the 65 women are listed in Table 6 (Appendix).

### *Obstetric trauma and sphincter defect*

The women reported 2.0 (IQR 2.0-3.0) vaginal deliveries. In addition, 7 (11%) women had undergone one caesarean section and 5 (8%) two caesarean sections. A third degree OASIS was reported by 27 women (42%) and a fourth degree OASIS by 38 (58%) women. Instrumental assisted deliveries were reported by 17 (26%). A median of 39 (IQR 25.5-44) years had passed since the OASIS.

The EAUS defect score was unavailable in 4 (6%) patients: In two patients the distal sphincter was not included in the EAUS data file and was thus impossible to score. The files were missing in the two patients from St Olav's Hospital. An isolated EAS defect was identified in 46 (75%) patients and a combined EAS and IAS defect in 12 (20%) women, and the mean EAUS defect score was 2.7 (SD 1.8), median 2.0 (1.0-4.0). Two (3%) women had no structural defects after primary repair and one (2.%) woman following secondary repair. Eight (12%) women had been treated with a secondary sphincter repair between 3 and 17 years prior to enrolment.

### *Faecal incontinence*

A total of 54 (83%) women reported FI for more than 5 years. Mean St Mark's score was 17.3 (SD 3.2). FI with urgency was reported by 49 women (75 %), passive FI was described by three (5 %) women and mixed FI by 13 (21 %). The median number of weekly FI episodes

was 4.5 (IQR 2.0-10), bowel-emptying episodes was 15.5 (IQR 10-23) and urgency episodes was 6.5 (IQR 4.0-12.5).

### *Quality of life*

The generic QoL was measured using EQ-5D. The mean EQ-5D VAS score was 63.2 (SD 20.8) and the EQ-5D index was 0.72 (SD 0.19). The four domains (lifestyle, coping, depression and embarrassment) of the disease specific Rockwood FIQL scale reflected the burden of FI with mean values of 2.56 (SD0.81), 1.71 (SD 0.58), 2.93 (SD 0.92), 1.81 (SD 0.62), respectively.

### *Urinary incontinence*

Concomitant UI defined as ICIQ-UI-SF score higher than zero was present in 47 women (72 %). Figure 8 shows the distribution depending on severity of UI in all of the women. The overall ICIQ-UI SF score was 8.7 (SD 6.8) and 11.6 (SD 5.2) in the 47 women reporting UI. Urge UI was reported by 36/47 (77%). A total of 25/65 (38%) women had undergone previous surgery for UI, including 17 TVT (trans vaginal tape) operations. In five women UI ceased after the TVT operation.

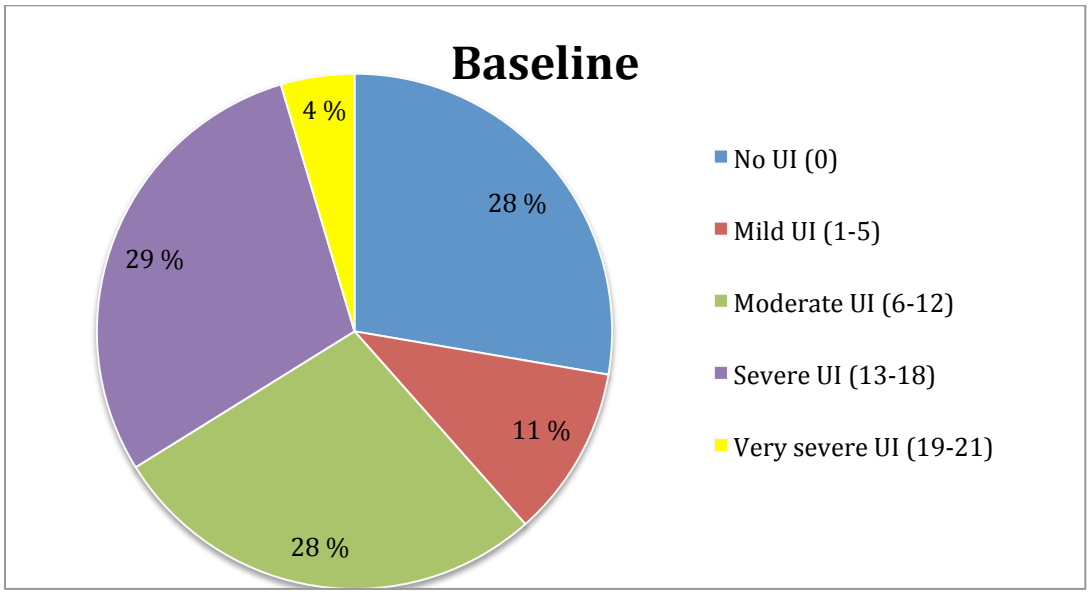



***Figure 8*** *The severity of urinary incontinence (UI) at the time of inclusion in all of the 65 women. A total of 47 (72%) women reported UI, 18 (28%) reported isolated faecal incontinence.*

### *Sexual function*

Nearly half (n=31,48%) of the patients were sexually active. Of the sexually active women, 9 (29%) reported pain and 23 (74%) reported other problems related to sexual activity, primarily fear of FI (n=20, 65%) during intercourse. Other concerns were general depression, vaginal dryness and appearance of external genitalia. Nineteen (61%) of the sexually active women stated that their sexual problems were bothersome.

## Paper I- PNE

A total of 63 women underwent a 3-week PNE period at UNN from February 2012-February 2014 (Figure 9).

### Faecal incontinence

Fifty-six (89%) of the 63 women were responders with a successful PNE. Responders achieved a 94.5% reduction in weekly FI episodes, from median (IQR) 4.8 (2.0-11.0) to 0.5 (0-2.0, $p<0.001$). Twenty-nine women (45 %) reported no FI episodes during PNE. The reduction in weekly urgency episodes was 82%, from 6.5 (4.0-12.5) to 1.0 (0-3.0, $p<0.001$). Urgency disappeared in 18 of the 56 (32%) responders.

### Relation between baseline factors and outcome

There were some differences in baseline characteristics between the responders and non-responders, which are presented in (Table 7, appendix). Responders were more likely to be postmenopausal ($p=0.03$), with higher BMI ($p=0.007$), higher baseline St Mark's score ($p= 0.004$) and concomitant UI ($p=0.034$). The extent of the sphincter defect did not differ between responders and non-responders ($p= 0.11$).

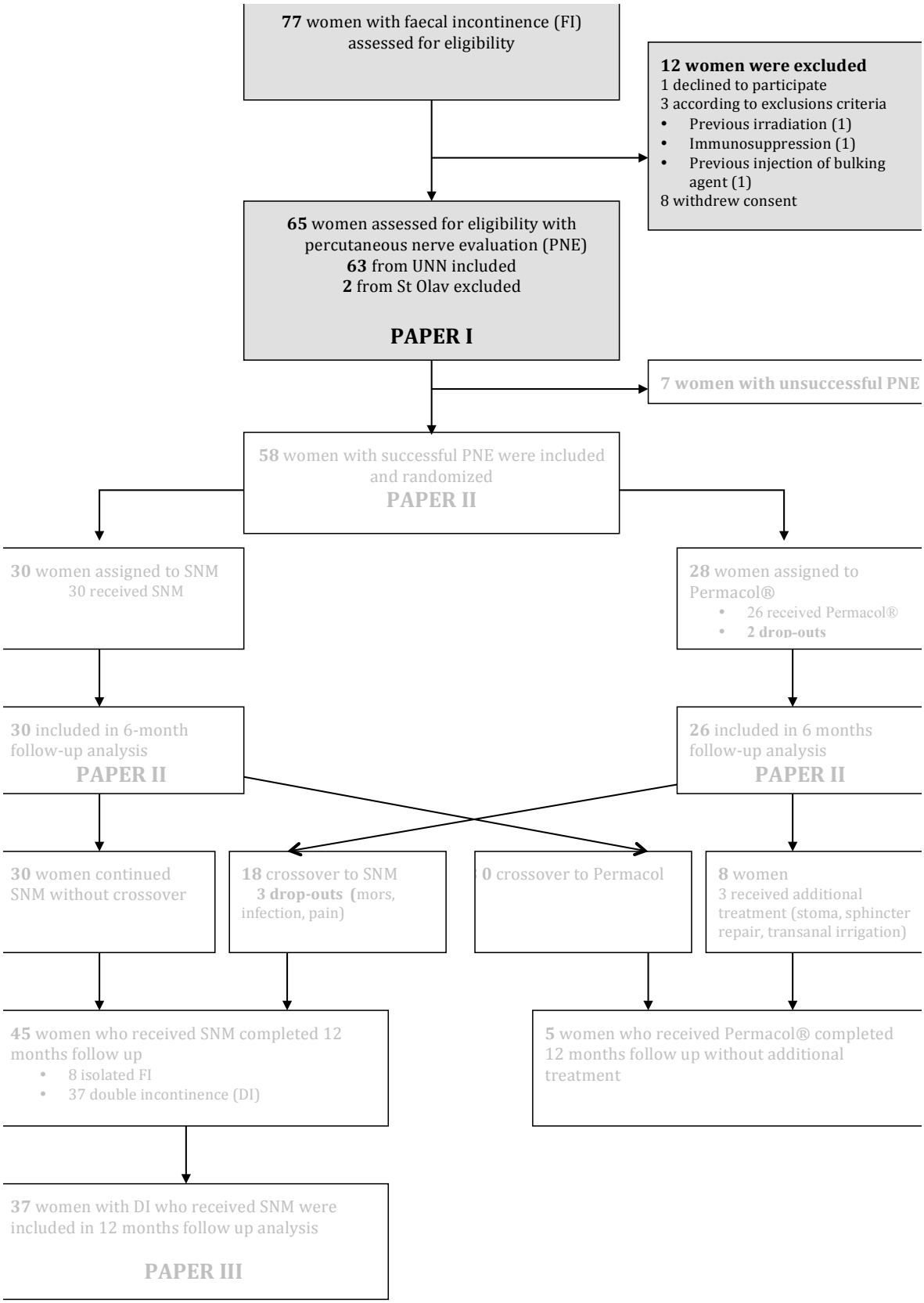



***Figure 9*** *Flowchart of the enrolment of the 63 participants in paper I*

In the multivariable logistic regression model, baseline St. Mark's score was the only variable significantly associated with successful PNE, with an odds ratio of 1.47 (95% CI 1.01-2.14, p=0.046) (Table 8). Concomitant urge UI (p= 0.004) and BMI (p=0.03) were the two baseline factors significantly associated with per cent of reduction in weekly FI episodes in the multivariable linear regression model (Table 9).

| | **Univariable regression model (Crude)** | | | **Multivariable regression model (adjusted*)** | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | P-value | OR | 95% CI | P-value |
| Menopausal status | 6.83 | 1.20-39.1 | **0.031** | 3.32 | 0.37-30.1 | 0.29 |
| Body mass index (kg/m$^2$) | 1.37 | 1.03-1.81 | **0.029** | 1.48 | 0.91-2.43 | 0.12 |
| St. Mark's score (0-24) | 1.51 | 1.11-2.05 | **0.009** | 1.47 | 1.01-2.14 | **0.046** |
| Urge UI | 10.0 | 1.13-88.9 | **0.039** | 4.62 | 0.38-55.7 | 0.23 |

***Table 8*** *Odds ratios of successful PNE defined as 50% or more reduction in weekly faecal incontinence episodes using logistic regression models.*Mutually adjusted for variables significant from univariable model. OR=Odds ratio, CI= Confidence interval*

## Adverse events

Pain during PNE was inversely related to efficacy (reduction in FI episodes during PNE) (R=-0.29, p=0.02) and also related to unfavourable outcome in the adjusted linear regression model (p=0.046). Pain was also related to low BMI as eight of 22 (36%) with a BMI of less than 25 reported pain compared with 6 of 41 (15%) with a BMI>25 (R=0.25, p=0.049).

| | **Univariable regression model (Crude)** | | | **Multivariable regression model (adjusted*)** | | |
|---|---|---|---|---|---|---|
| | Beta | 95% CI | P-value | Beta | 95% CI | P-value |
| Urge UI | 26.5 | 12.9-40.2 | **<0.001** | 20.0 | 6.6- 33.5 | **0.004** |
| Body mass index (kg/m$^2$) | 2.1 | 0.6-3.6 | **0.007** | 1.5 | 0.1-2.9 | **0.03** |
| FIQL Coping (0-4) | -14.3 | -27.5 to -1.1 | **0.03** | -3.8 | -17.6-10.0 | 0.6 |
| Eq-5D VAS (0-100) | -0.4 | -0.7- 0.001 | *0.051* | -0.2 | -0.6-0.2 | 0.3 |
| Pain | -20.9 | -38.2- 3.5 | 0.02 | -15.6 | -31.5-0.4 | **0.046** |

***Table 9*** *Linear regression coefficients for the association between efficacy defined as percent reduction in weekly faecal incontinence episodes as dependent variable and urge urinary incontinence, Body Mass Index (kg/m$^2$), QoL and pain. *Mutually adjusted for the listed variables. Beta=Linear regression coefficients, CI=Confidence interval*

## Paper II RCT SNM versus Permacol®

A total of 58 women were randomly assigned to receive SNM (n=30) and injection of Permacol® (n=28). All were available for analysis at six months except for the two patients who withdrew consent before receiving Permacol® (Figure 10). Primary and secondary outcomes are available in Table 10 (appendix).

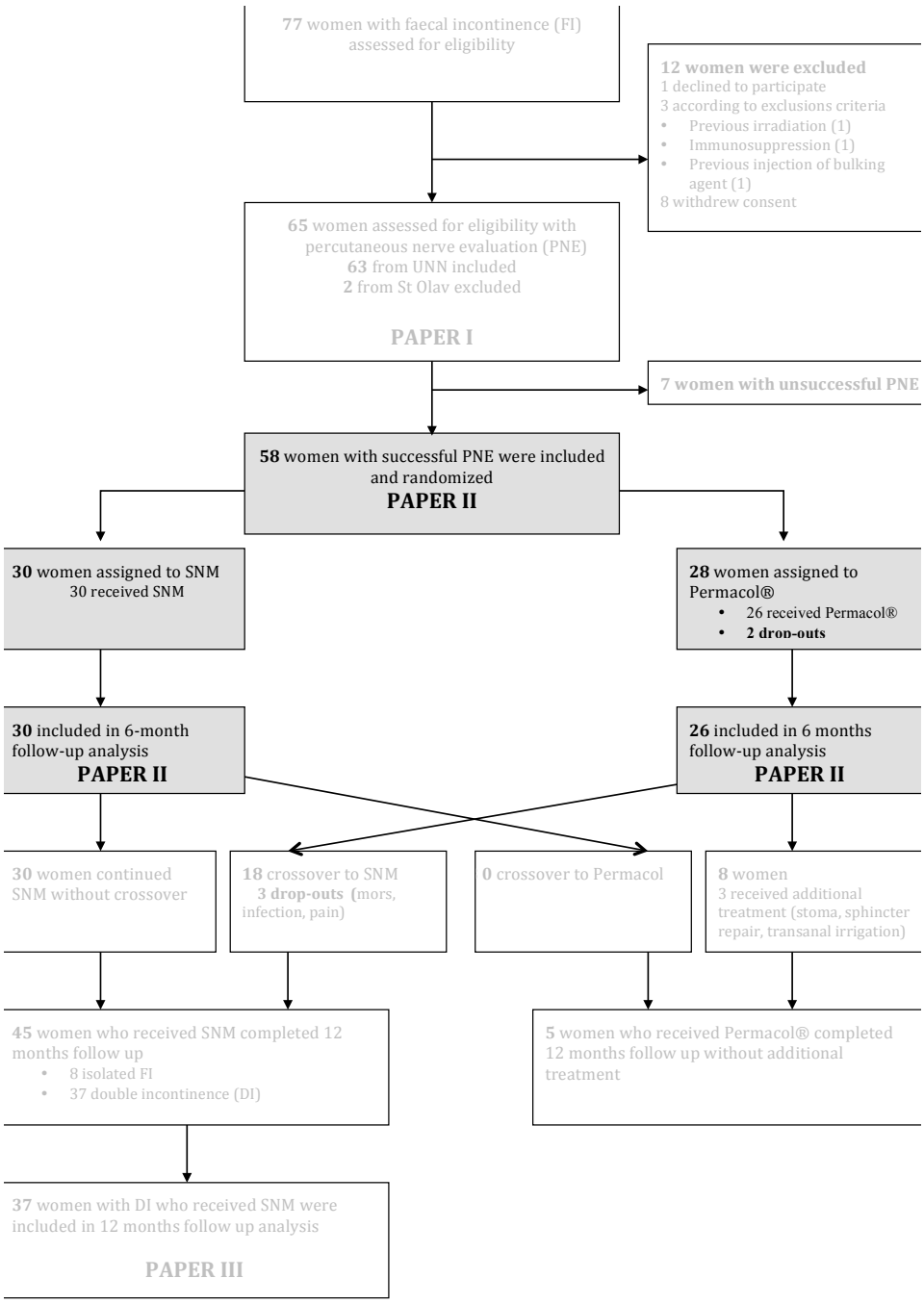



***Figure 10*** *Flow chart of the enrolment of the 58 women in the randomized controlled trial (paper II)*

## Faecal incontinence

The reduction in the St. Mark's score between baseline and 6 months was 11.2 (SD 5.3) in the SNM group versus 2.3 (SD 5.0) in the Permacol® group, resulting in a treatment difference of 8.9 (95% CI 6.1-11.7, p<0.0001) in favour of SNM (Figure 11).

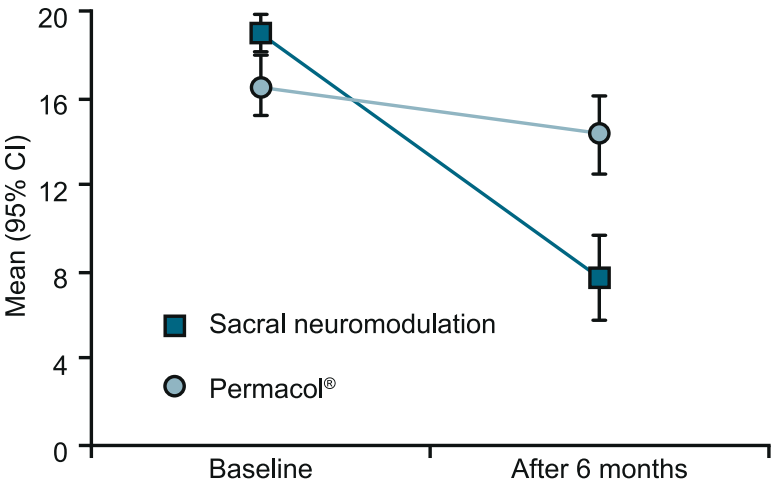



***Figure 11*** *The reduction of St Mark's score from baseline to six months in the SNM group compared to the Permacol® group. Illustration by Rod Wolstenholme.*

A 50% or greater reduction in weekly FI episodes was accomplished in 28 (93%) women after SNM compared to nine (32%) following Permacol® application (p=0.001). Complete continence without weekly FI episodes, was described by 17 (57%) after SNM compared to three patients (11%) after Permacol® (p<0.001). Weekly urgency episodes disappeared in 18/29 (62%) women after SNM compared to 6/25 (24%) women following Permacol® (p= 0.007).

## Quality of life

SNM was superior to Permacol® regarding the four domains of the FIQL, including lifestyle (0.90, 95% CI 0.50-1.30, p<0.001), coping (1.05, 95% CI 0.62-1.47, p<0.001), depression (0.52, 95% CI 0.16-0.87, p=0.005) and embarrassment (0.95, 95% CI 0.50-1.40, p<0.001). Women with SNM achieved an improvement in their EQ-5D™ global health score (0-100) of 11.1 (SD 21.9) compared to 2.7 (SD17.8) in women treated with Permacol®, but the difference (8.4, 95% CI -2.4-19.3) was not significant (p=0.12). The difference in the EQ-5D index (0.031, 95% CI -0.14-0.07; p=0.55) was likewise not significant.

Overall, 23 (77%) women in the SNM group were satisfied with their treatment after 6 months compared to only 3 (11%) satisfied women in the Permacol® group (p<0.001).

### Urinary incontinence

Concomitant UI was reported by 27 (90%) in the SNM group and 16 (61%) in the Permacol®-group. The mean reduction in the ICIQ-UI-SF score in the SNM– group was of 5.3 (SD 5.8) compared 0.27 (SD 5.4) in the Permacol®-group, giving a difference in score of 5.0 (95% CI 1.97-8.02 p=0.002) in favour of SNM; when adjusting for the baseline ICIQ-UI-SF score, the difference was 3.0 (0.2-5.9, p=0.037).

### Sexual function

There was some imbalance in baseline sexual activity, as there were 19 (63%) sexually active women in the SNM group and 8 sexually active women (29%) in the Permacol® group. There was no significant difference after 6 months in the number of sexually active women (16 in the SNM group versus 6 in the Permacol® group; p=0.80). Overall at baseline, 14/19 (74%) in the SNM group had a sexual complaint compared to 7/8 (88%) in the Permacol® group. After six months, 5/16 (31%) in the SNM group had a sexual complaint compared to 5/6 (83%) in the Permacol® group (p=0.26). The number of women reporting bothersome sexual problems from baseline to 6 months changed from 11/19 (58%) to 4/16 (25%) in the SNM group compared with a change from 6/8 (75%) to 5/6 (83%) in the Permacol® group (p=0.061, in between group difference).

### Adverse events

There were 9 (35%) minor adverse events in the SNM group compared to seven (27%) in the Permacol® group (p=0.77). No infections were detected in either of the groups. After SNM, one patient reported pain related to the IPG and one described painful stimulation in the extremities. Five women reported a deterioration of urinary function, which resolved after resetting of the IPG. Two women were referred to specialists for further investigation after 6 months because of deterioration of UI. The IPG was reset during follow-up in 17 (57%) patients, including an adjustment of the amplitude from 1.05 (SD 0.48) mA to 1.41 (SD 0.85) mA and readjustment because of pain (n=1) or deterioration of urinary function (n=7).

Two (8%) women did not receive a second injection with Permacol® because of anal pain after the first injection, and another woman refused because of lack of effectiveness. Five (19%) reported mild symptoms of obstructed defecation that did not require treatment.

### Additional analysis

In the best-case scenario for Permacol®, the four allocated to the Permacol® group were given a reduction of St Mark's score of 16. This resulted in an estimated reduction of St Mark's score of 4.1 (95% CI 1.7- 6.6) in the Permacol®-group compared to an estimated reduction of St Mark's score of 10.1 (95% CI 7.9-12.3) in the worst case scenario in the SNM-group. The difference of 6.0 (95% CI 2.7-9.3) did not affect the highly significant effectiveness of SNM compared with Permacol® (p=0.001). The sensitivity analysis, excluding the two patients from St Olav's Hospital because of imbalanced recruitment between the two centres, did not affect the outcome with a difference in the effectiveness of 8.8 (95% CI 6.03-11.6) p<0.001.

## Paper III Double incontinence

A total of 48 women received SNM, of whom 30 were randomly assigned to SNM and 18 crossed over after primary allocation to injection of Permacol® after successful PNE. Three were lost to follow-up as described in the study overview. The eight women with isolated FI were excluded, providing 37 women with DI available for analysis 12 months after SNM (Figure 12).

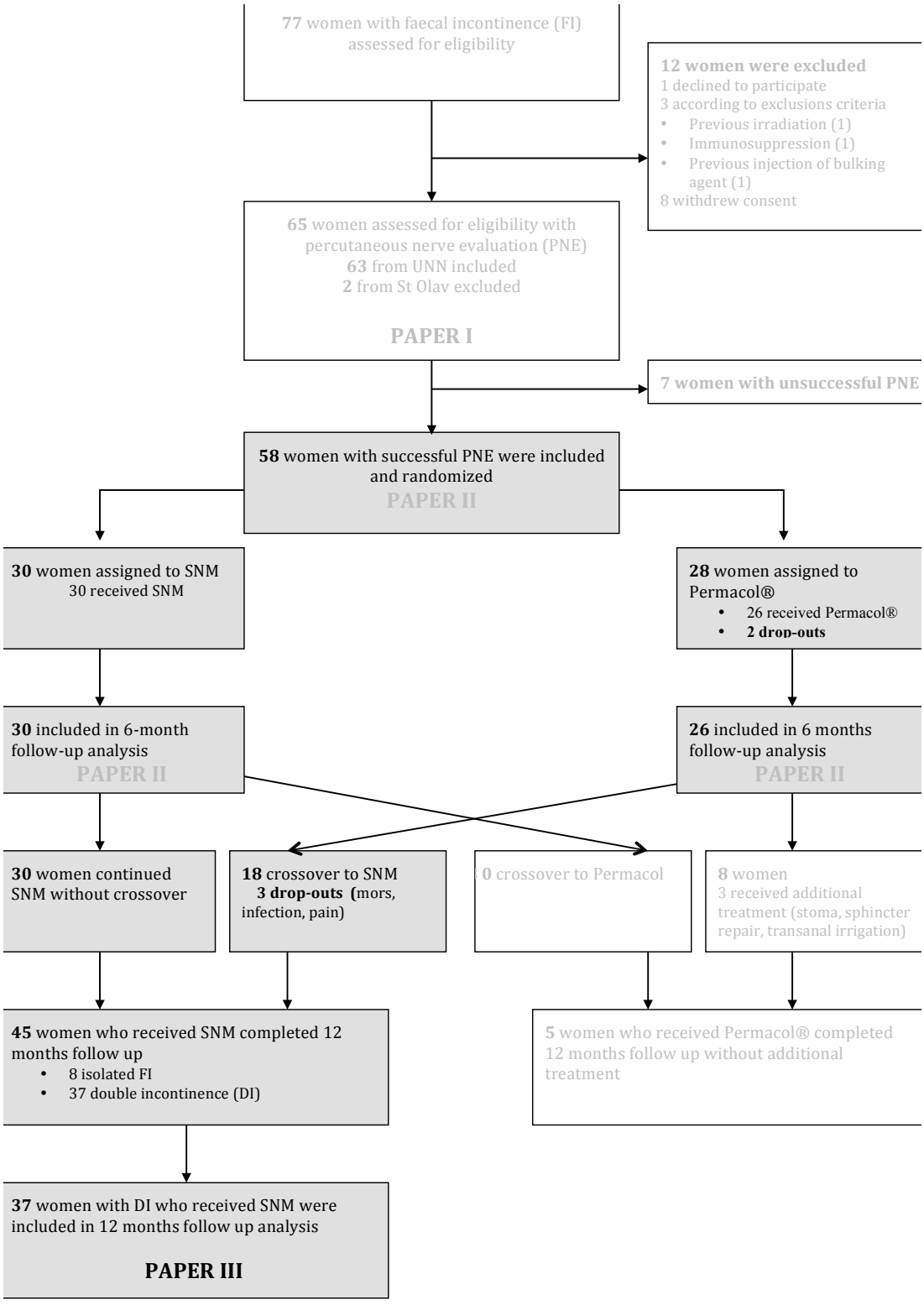



***Figure 12*** *Flow chart illustrating the assignment of the 37 women with double incontinence following OASIS who received SNM (Paper III).*

### Urinary incontinence

The overall reduction in ICIQ-UI-SF score from baseline to 12 months was 5.8 (95% CI 3.7-8.0), from 12.4 (SD 5.1) to 6.5 (SD 5.8) ($p<0.001$) (Table 9). The change in ICIQ-UI-SF score for each of the 37 women is shown in Figure 13.

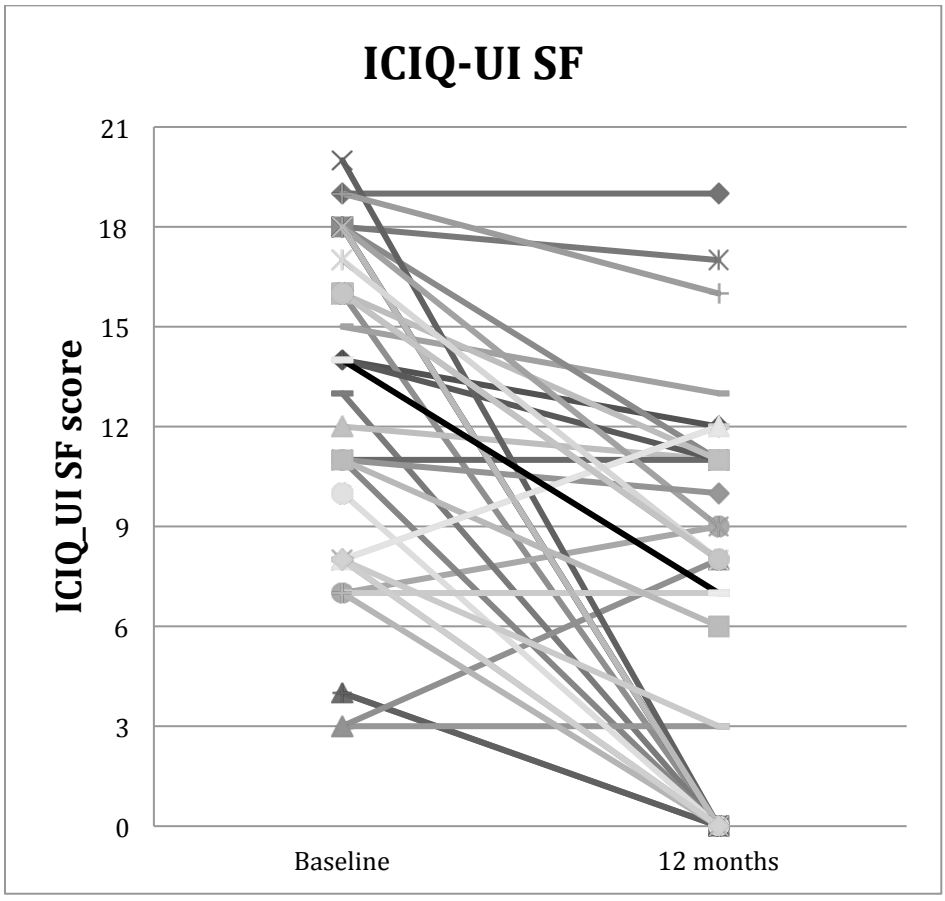



***Figure 13*** *Change in ICIQ-UI-SF score from baseline to 12 months after SNM for each of the 37 women with combined faecal and urinary incontinence (double incontinence). ICIQ-UI SF= International Consultation on Incontinence Questionnaire Urinary Incontinence Short Form. It ranged from 0 (continent) to 21 (complete incontinence).*

A significant shift in the severity of UI was also observed, with 16 (43%) women reporting severe UI at the time of inclusion compared to 4 (11%) 12 months after SNM (p<0.001). Another 13 (35%) women reported no UI after 12 months (p<0.001) (Figure 14). Urgency disappeared in 14 of 33 (42%) women (p=0.001).

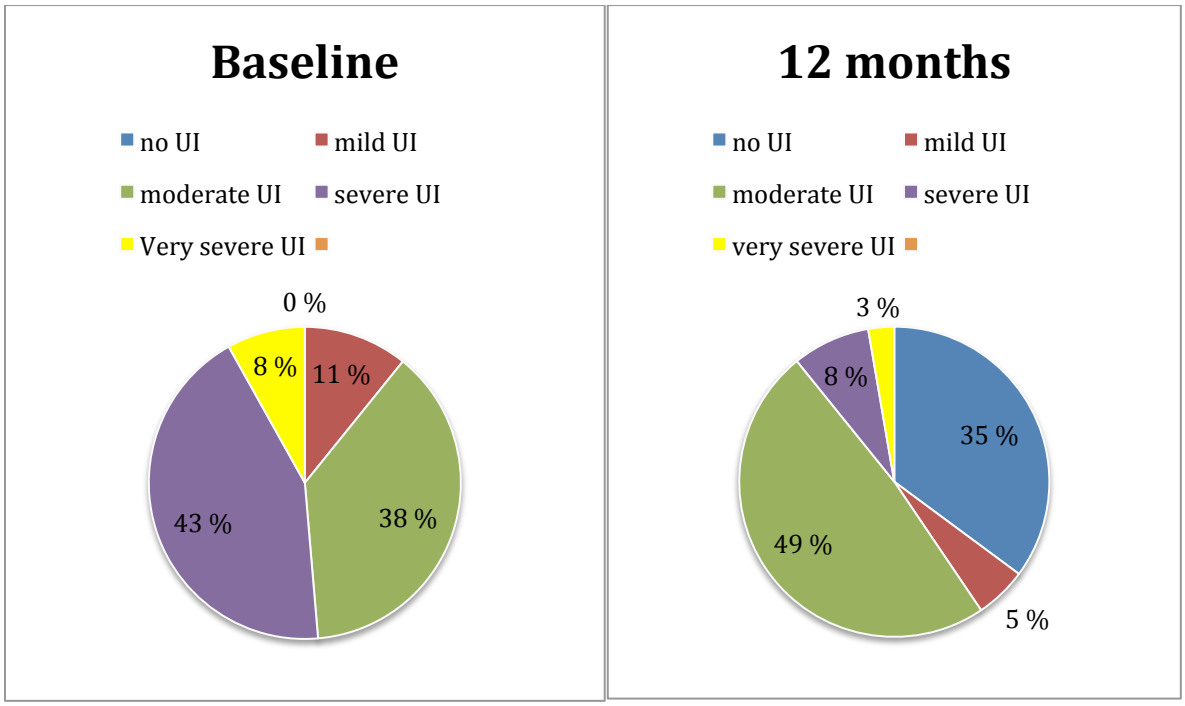



***Figure 14*** *The shift in severity of urinary incontinence (UI) from the time of inclusion compared to 12 months after SNM in the 37 women with double incontinence following OASIS. Note that all reported concomitant UI at baseline compared to 13 (35%) with no UI after 12 months.*

### Faecal incontinence

The mean reduction in the St Mark's score from baseline to 12 months was 10.6 (95% CI 8.6-12.7, p<0.001), from 17.8 (SD 2.6) to 7.1 (SD 5.3) (Table 11, appendix). Faecal urgency was reported by one (97%) compared with 13 (33%) at 12 months (p<0.001). Complete continence without weekly FI episodes, was reported by 23 (62%) (p<0.001). No improvement was reported by 3 (8%), giving a success-rate of more than 90% for FI in the patients with DI compared to 81 % for UI.

### Quality of life

The mean EQ-5D VAS score changed from 59 (SD 20.4) at baseline to 73 (SD 17.8) at 12 months, giving an overall improvement in general health of 15 (95% CI 5.6-24.9, p=0.003). The change in the EQ-5D index was not significant (0.047, 95% CI -0.04-0.13, p=0.26). The

bothering component of the ICIQ-UI-SF score (0 best-10 worst) was reduced from 6.2 (SD 3.3) at baseline to 3.3 (SD 3.4) after 12 months, giving a mean difference of 2.9 (95% CI 1.6-4.2). All four domains of the Rockwood FIQL scale (0 worst, 4 best) changed significantly: lifestyle changed by 1.1 (95% CI 0.71-1.4), coping by 1.2 (95% CI 0.89-1.5), embarrassment by 1.3 (95% CI 0.89-1.6) and depression by 0.67 (95% CI 0.38-0.95) (Table 11, appendix).

### Sexual function

Of the 23 (59%) women who reported being sexually active at baseline, 17 (74%) were sexually active 12 months after SNM (p=0.25). Among sexually active women, sexual function improved. Pain during intercourse was reported by eight (35%) at baseline compared with four (17%) after 12 months (p=0.046). Fear of incontinence during intercourse was defined as a major problem by 17 (74%) at the time of inclusion, but only by 11 (46%) 12 months after SNM (p=0.034). However, the change from 14 (61%) to 10 (59%) women stating that their sexual problems were bothersome was not significant (p=0.32).

### Logistic regression model

The only baseline factor related to a successful outcome in terms of reduction of the ICIQ-UI-SF score 12 months after SNM, was a higher baseline ICIQ-UI-SF score, with an OR per score points of 1.23 (95% CI 1.04-1.47, p=0.018).

## SUPPLEMENTARY ANALYSIS NOT PRESENTED IN THE ORIGINAL PAPERS

### Predictors SNM (12 months, n=45)

Of the 45 women who had SNM at 12 months follow-up, 3 were non-responders. Responders were more likely to report concomitant UI and low score on the embarrassment item of the Rockwood FIQL-scale, but the factors were not significant in the regression model.

## Predictors Permacol® (6 months, n=33)

In addition to the 26 women randomly assigned to Permacol®, the seven women with an unsuccessful PNE received Permacol®. Only five women randomly assigned to Permacol® and four women with unsuccessful PNE continued without additional treatment after 6 months. The nine responders had higher baseline score of the embarrassment item of Rockwood FIQL scale . They were less likely to report concomitant UI as only 2/9 (22%) responders reported UI compared to 17/24 (71%) non-responders, with an OR of 8.5 (95%CI 1.403-51.48, p=0.032). Table 12 shows the OR of response to Permacol® using a multivariable logistic regression models.

| | **Univariable regression model (Crude)** | | | **Multivariable regression model (adjusted*)** | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | P-value | OR | 95% CI | P-value |
| FIQL Embarrassment | 8.99 | 1.53-52.7 | **0.015** | 5.62 | 0.96-32.7 | 0.056 |
| Urinary Incontinence score (ICIQ-UI-SF ) | 0.83 | 0.70-1.01 | **0.027** | 0.88 | 0.72-1.12 | 0.23 |

***Table 12.*** *Odds ratios of successful treatment with Permacol® (n=33) using logistic regression models. *Mutually adjusted for variables significant from univariable model. OR=Odds ratio, CI= Confidence interval*

## Combination of SNM and Permacol®

There were no significant difference in St Mark's score at 12 months between the group who received SNM (n=30) and those who received the combination of Permacol® and SNM (n=15), (1.9, 95% CI -1.5-5.3, p=0.27).

# DISCUSSION

## Paper I

This is one of the largest prospective series in which efficacy during PNE, using a tined lead and the Verify® EPG, was related to baseline factors in women with FI following OASIS. The vast majority had successful outcomes; nine of ten were responders with a reduction in weekly FI episodes of more than 90%. The baseline St. Mark's score was the sole factor predicting PNE outcome in the multivariable logistic regression model. In the multivariable linear regression model, concomitant UI and a higher BMI were related to greater reduction in weekly FI episodes. Pain during PNE was related to unfavourable outcome, whereas the extent of the sphincter defect did not affect the outcome[103].

A 90 % reduction of FI episodes during PNE, are shown to be predictive of patient satisfaction with SNM [104] and with a lower probability of failure of SNM over the long term [63-65]. Our PNE success rate is higher than the 66.8% success rate from the European SNS outcome study group [63] but similar to the results of a recent review including 119 women with FI and sphincter disruption [85].

### Baseline factors and efficacy

#### *St Marks score and concomitant urinary incontinence*

St. Mark's score was a positive predictor of successful PNE. Except for the importance of loose stool consistency [101], the severity of FI at baseline has not been related to PNE outcome [63, 64, 105, 106]. A greater improvement in postmenopausal women with more severe FI, may be explained by the fact that these women have more to gain than younger patients with a more recent repair, a better recovery capacity and less comorbidity. This idea is supported by a meta-analysis in which greater improvement after SNM was observed in postmenopausal women with severe FI [107]. Moreover, given that sphincter injury is only one factor in the complexity of FI [38], a higher St. Mark's score may express more severe and complex damage to the pelvic floor. The finding that concomitant UI was correlated to a greater reduction in weekly FI episodes supports this. It is possible that SNM works better in

severe FI and concomitant UI because it has the potential to modify all aspects of the coordinated neuromuscular functions required for both urinary and bowel control [38, 62] ,

***BMI***

A higher BMI was associated with a greater reduction in weekly FI episodes during PNE. The literature is inconsistent regarding an assumed association between BMI and efficacy during PNE both for FI and UI, but increased rates of reoperations and complications have been described in SNM patients with lower BMI or change in BMI [108-112]. While series exploring predictors of SNM for FI have failed to show an association between BMI and outcomes [64, 105, 106], a relation between low BMI and unfavourable outcome as shown in our study has also been demonstrated in urological patients [108, 109, 112] and children [110]. Bilateral migration of tined leads in a thin patient is thoroughly discussed by Kessler et al in 2005 [112]. A possible mechanism may be that the lead is more prone to displacement with subsequent reduced efficacy in thinner patients who have less lean muscle and subcutaneous tissue to anchor the tined lead [112]. Additional factors responsible for lead migration could be distension of pelvic organs and the stiffness of the tined lead [112]. Variations in the lead position may even generate painful stimulation. If pain necessitates a reduction in amplitude, the efficacy can be reduced [113]. Finally, leaner patients with less protective tissue might be more physically active during the PNE period and thereby more susceptible to lead breakage following minor trauma. This mechanism has been described in a paediatric population [110].

***Pain***

Previous reports [64, 114] have not elucidated the manner in which pain affects PNE outcomes although leg pain is a documented cause of the long-term failure of SNM despite attempts to resolve the problem by reprogramming [38, 65]. Pain during the PNE period is unpleasant for the patient, and reducing the amplitude to resolve the undesirable stimulation is likely to reduce efficacy [113]. If pain is recognized during lead placement although a low motor threshold is achieved, repositioning of the lead or changing the foramen should be considered.

### *Sphincter defect*

The extent of sphincter defect expressed with the EAUS defect score, was not related to outcome. The literature is conflicting regarding the importance of the extent of sphincter defect and PNE outcome. Some researchers observe no relation, whereas other studies have suggested that an EAS defect increases the risk of PNE failure without excluding patients from SNM. Caution should be exercised when drawing conclusions from our limited material because few women had large defects. Nevertheless, our results show that the presence of a sphincter defect does not preclude PNE.

## Paper II

This is the first RCT to compare the effectiveness of SNM and injectable bulking agents for FI following OASIS. SNM was superior to Permacol® at six months compared with baseline in terms of reducing the St Mark's score and ICIQ-UI-SF score, changing of FIQL score and improving patient satisfaction [115].

### Faecal incontinence

The primary outcome, the reduction of the St Mark's score, clearly illustrated the difference in effectiveness between the two treatments in favour of SNM. The effectiveness of SNM was similar to findings from several published case series and some RCTs, with regard to reducing symptom scores, number of weekly FI episodes, achieving complete continence in more than a third of patients, improving the ability to defer defecation, all categories of FIQL score when assessed, and achieving effectiveness unrelated to the extent of the sphincter defect [38, 50, 85]. The effectiveness of Permacol® was rather disappointing compared with three series of Permacol® showing success rates of 53%, 56% and 72% [67, 69, 70], but similar to a pilot trial comparing perianal injection of 15 ml Permacol® and Bulkamid® [116].

St Mark's score below 9 after treatment is assumed to be clinically significant and associated with improved QoL [87]. This outcome was achieved after SNM, but not after Permacol® application. The patients in the SNM-group achieved corresponding improvements of their FIQL scores compared to no improvement following Permacol®. The lack of clinical improvement of Permacol® was further demonstrated by the fact that only 11% of the women were satisfied with Permacol® after 6 months compared to approximately three-quarters of the women in the SNM group.

### Concomitant urinary incontinence

Three-quarters of the women reported concomitant UI compared to a previous reported prevalence of 30%- 50% [7, 80, 117]. The high prevalence of concomitant UI may be explained by the systematic assessment using a validated questionnaire with a low cut-off value defining UI. SNM was superior to Permacol® in the treatment of concomitant UI in terms of reduction of the ICIQ-UI-SF score.

We did not expect Permacol® to improve concomitant UI as Permacol® acts locally in the anal canal and prevents FI by sealing the anal canal. In contrary, because SNM originally was developed for UI [118], some improvement of concomitant UI was predictable [51, 62, 118]. The study was not powered to detect differences of improvement in subgroups, but SNM may be an appropriate treatment for women with DI [49, 80, 119, 120]. SNM for DI is further discussed in paper III.

### Sexual function

Two thirds of the patients were postmenopausal, half of the women were living along and the majority reported a severe symptom load of FI with major impact on QoL. In the SNM group, sexual complaints and bothersome sexual problems decreased, but the differences between the groups were not significant.

Assessing female sexual function is challenging and changes after intervention are difficult to interpret. Many patients suffering from anxiety and depression avoid intimate relationships and choose to live alone, indicating the close relationship between sexual function, UI, FI and QoL [29, 121]. The RCT was not powered to detect differences of improvement in the subgroups, considering the imbalance between the groups regarding sexual activity. The statistical tests relate to only a small subgroup of the randomized patients, making the analysis and comparison between the groups rather difficult [115].

### Placebo

The clinical relevance of bulking agents has been questioned in a recent Cochrane review [51]. A minority of the women who received Permacol® reported alleviation of symptoms. The supplementary analysis indicated that these women had a minor symptom-burden, with

no UI and with better QoL scores. At least three different RCTs have shown that one-third of the patients who received sham-treatment for FI was considered as responders [68, 122, 123]. The placebo effect should not be neglected [51]. It is challenging to determine whether the effectiveness of Permacol® observed in one-third of the patients represent the placebo-effect or a potential group highly selected patients who might benefit from treatment with Permacol® [124]. However, Permacol® has no place in the treatment algorithm for severe FI and concomitant pelvic floor dysfunction following OASIS despite its simplicity, minimal invasiveness and low costs, as recently stated by an editorial [53].

## Paper III

The women treated with SNM for FI after OASIS also experienced a reduction of UI when present. The improvement of concomitant UI in terms of reduction of the ICIQ-UI-SF score was observed in three quarters of the women. UI and urgency disappeared in one-third of the patients. Higher baseline ICIQ-UI-SF scores predicted successful outcome. More than 90% reported improved FI in terms of reduction of St Mark's score. Sexually active women reported less pain and fear of incontinence during intercourse and increased QoL.

### Double incontinence

Concomitant UI improved in this group of mainly postmenopausal women with severe FI resistant to conservative treatment. The results were comparable for SNM for UI in general, with improved UI in two-thirds of patients after two years [125, 126]. A retrospective series including 57 patients with DI showed that UI improved in 78% of the patients and FI in 96% [119]. A discrepancy in success-rate for UI from 20 to 100% in a recent review on SNM for DI was explained by variation in patient selection and use of different outcome measures [80]. Success rates for FI are recognized to be superior to success rates for UI after SNM [38, 118].

Some of the women reported deterioration of UI despite successful treatment of FI. Unfavourable changes in urinary function following SNM for FI have been described previously and can be restored by readjustments of the IPG [114]. Deterioration of UI may also reflect conditions requiring additional management other than SNM [80]. A third possibility is that successful treatment of FI changes the perception of the remaining symptoms of UI, resulting in a higher bother score.

A higher ICIQ-UI-SF score predicted successful outcome for the treatment for UI similar to the findings from paper I where concomitant UI was shown to be associated with successful outcome of PNE [103]. This may indicate that severe concomitant UI is a predictor of successful outcome after SNM.

### Sexual function

Among sexually active women, sexual function improved in term of less pain and fear of FI. However, the change in women stating that their sexual problems were bothersome was not significant.

A recent published review on the impact of SNM on female sexual function reported improved sexual function in all included studies, but different outcome measures were used [127]. In the present study, a questionnaire developed by an expert group on OASIS was chosen [79]. The expert group highlighted the importance of assessment of bothersome sexual problems to avoid over-diagnosis of sexual complaints. This has to be considered when analysing outcome, and cautions is advocated when drawing conclusions on the effectiveness of SNM on sexual function [128].

### Quality of life

Double incontinence is a more severe manifestation of pelvic floor dysfunction and is associated with a greater impact on QoL than the two conditions separate [129, 130]. DI causes psychological distress, and many women suffer from anxiety and depression [81, 102, 129, 130]. This is consistent with our findings with low disease specific QoL scores at baseline. Generic and disease-specific QoL, including all four domains of the Rockwood FIQL scale and the bothering component of ICIQ-UI-SF score, improved 12 months after SNM. This is consistent with previous findings were bowel and urinary related QoL and global health improved after SNM in women with pelvic floor dysfunction [117, 119].

# CONCLUSIONS AND CLINICAL IMPLICATIONS

Different clinical questions and aspects of treatment for FI and concomitant pelvic floor dysfunction in women with a history of OASIS have been investigated:

## Faecal incontinence

The vast majority of the women had successful outcome after PNE, and a higher St Mark's score predicted successful outcome of PNE. Women who received SNM achieved St Mark's score below 9, which is assumed to be clinically significant and associated with improved QoL. FI and urgency completely disappeared in more than one third after SNM compared to a rather disappointing effectiveness of Permacol®.

SNM was superior to Permacol®, with three-quarters of the women were satisfied with SNM compared to only 10% after Permacol®. Considering the 30 % placebo effect in the treatment of FI [68], we conclude that Permacol® has no place in the treatment algorithm for substantial FI following OASIS.

## Sphincter defect

No association between the extent of the sphincter defect assessed with EAUS defect score and outcome during PNE, after SNM or after Permacol® was revealed. SNM should be considered as the first-line treatment for all women with FI following OASIS after failure of conservative management, regardless of the extent of sphincter defect, in the absence of other indications for perineal reconstruction [38, 64, 85, 106, 107, 131, 132].

## Quality of life

The burden of severe FI and pelvic floor dysfunction causes psychological distress. Treatment of FI and concomitant pelvic floor dysfunction improves patients satisfaction, disease specific and generic Qol. SNM significantly improved QoL compared to no improvement following Permacol®.

### Urinary Incontinence

Three quarters of the women reported DI. UI was successfully treated with SNM in terms of reduction of ICIQ-UI-SF, complete continence and disappearance of UI in one third, compared to no change after Permacol®. Concomitant urge UI was related to successful outcome of PNE and higher baseline ICIQ-UI-SF scores predicted successful outcome after SNM.

SNM seems to be a suitable treatment for the majority of the women with DI. Evaluating UI with a simple questionnaire like ICIQ-UI-SF can be valuable for colorectal surgeons when deciding treatment for severe FI following OASIS.

### Sexual function

Only half of the women were sexually active, reflecting the complexity and burden of pelvic floor dysfunction. Sexually active women reported less pain and fear of incontinence during intercourse 12 months after SNM, but bothersome sexual problems did not change significantly. Assessment of bothersome problems has to be considered when analysing change in pelvic floor function, and caution is advocated when drawing conclusions on the effectiveness of any surgical treatment on sexual function.

# FUTURE RESEARCH AND PERSPECTIVES

### *Outcome*

An international initiative is warranted to achieve consensus on how to define FI and concomitant pelvic floor dysfunction, assess severity and report outcome. It is essential to possess robust outcome measures considering the bothering and burden of the symptoms and impact on QoL. Patients and health professionals may have different view on the weighted severity of different symptoms. When evaluating new treatments, overestimation of the benefits and underestimation of adverse events can be misleading. New treatment for FI should be rigorously evaluated in well-designed multicentre trials allowing safe and controlled introduction into current clinical practice.

### *Improvement of the SNM procedure*

The value of the PNE is under critical appraisal with the up-coming OneStage trial. A one-stage implant simplifies the patient's flow and management with one instead of two procedures requiring anaesthesia and an operating theatre. This could reduce the risk of implant infection, and patients could avoid restrictions related to an external system. A one-stage procedure will most likely save resources for the health system, although improved outcome after one stage compared to two stage is not expected.

The trial incorporates the standardization of SNM to ensure optimal placement of the tined lead along the nerve. Introducing the curved stylet, which was not used in this study, is an essential step. This may contribute to additional benefits and improved outcomes for the patients. The trial is also designed to investigate for a potential placebo effect of SNM in the treatment of FI.

***Perspective***

David Hume (1711- 1776) stated that medicine relies on facts and values. Values are not derived from facts or determined by the way the world is. Medicine depends on scientific facts, but health professionals need to value and choose between available options to accomplish high quality of diagnosis, tailored treatment strategies and care based on the individual's symptoms and expectations [133]. This may be facilitated by organization of care in pelvic floor units, ensuring a multidisciplinary approach to female pelvic floor dysfunction.

"The genius of the mind is to create a model of the world which is both useful and that, until it is examined more closely, deceives us that it is itself the world"[134].

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## Paper I-III

# Appendix

**Table 6**

| | Frequency | Mean(SD) | Median (IQR) |
|---|---|---|---|
| **Demographics** | | | |
| Age (years) | | 56.5 (12.5) | 59 (47-67) |
| Civilian status | | | |
| In a relationship | 43 (66%) | | |
| Alone | 22 (34%) | | |
| Body mass index (BMI, kg/m$^2$) | | 26.0 (4.4) | 25.2 (22.1-27.8) |
| History of a systemic disorders | 15 (23%) | | |
| Hypothyreosis | 3 (5%) | | |
| Arthritis including psoriasis arthritis | 4 (6%) | | |
| Sjogren´s Syndrome | 3 (5%) | | |
| Diabetes Mellitus (yes) | 5 (8%) | | |
| History of a neurological disorder (yes) | 10 (15%) | | |
| Operation for back injury | 5 (8%) | | |
| **Obstetric history** | | | |
| Postmenopausal status | | | |
| premenopausal | 20 (31%) | | |
| postmenopausal | 45 (69%) | | |
| Vaginal deliveries | | 2.5 (1.1) | 2 (2-3) |
| Instrumentation yes | 17 (26%) | | |
| Degree of OASIS | | | |
| 3th degree | 27 (42%) | | |
| 4th degree | 38 (58%) | | |
| EAUS defect score (0-7) | | 2.7 (1.8) | 2.0 (1.0-4.0) |
| No defect | 3 (5%) | | |
| EAS defect | 46 (71%) | | |
| Combined EAS/ IAS defect | 12 (18%) | | |
| Missing | 4 (6%) | | |
| **Faecal incontinence** | | | |
| St Mark's score (0-24) | | 17.3 (3.2) | 18 (15-20) |
| Type of FI | | | |
| Urge | 47 (72%) | | |
| Passive | 3 (5%) | | |
| Mixed | 15 (23%) | | |
| Bowel habit diary | | | |
| Weekly bowel emptying episodes | | 16.9 (8.8) | 15.5 (10-23) |
| Weekly FI episodes | | 7.5 (8.8) | 4.5 (2-10) |
| Weekly urgency episodes | | 8.9 (6.9) | 6.5 (4-12.5) |
| Duration of symptoms | | | |
| <1 years | - | | |
| 1-5 years | 11 (17%) | | |
| 6-10 years | 26 (40%) | | |
| >10 years | 28 (43%) | | |
| Previous secondary sphincter repair (yes) | 8 (12%) | | |
| **Quality of life (QoL)** | | | |
| EQ-5D | | | |
| EQ-5D VAS (0-100) | | 63.2 (20.8) | 70 (50-80) |
| EQ-5D index (-0.453-1) | | 0.72 (0.19) | 0.78 (0.66-0.83) |
| Rockwood faecal incontinence quality of life (FIQL, 0-4) | | | |
| Lifestyle | | 2.56 (0.81) | 2.7 (2.0-3.2) |
| Coping | | 1.71 (0.58) | 1.63 (1.22-2.11) |
| Depression | | 2.93 (0.92) | 3.14 (2.14-3.71) |

| | | | |
|---|---|---|---|
| Embarrassment | | 1.81 (0.62) | 1.67 (1.33-2.0) |
| **Urinary incontinence (UI)** | | | |
| ICIQ-UI-SF score (0-21) | | 8.7 (6.8) | 8.0 (0-15.0) |
| UI (yes) | 47 (72%) | | |
| Urge UI | 27 (57%) | | |
| Stress UI | 11 (23%) | | |
| Mixed UI | 9 (19%) | | |
| Operation for UI (yes) | 25 (38%) | | |
| Previous TVT (yes) | 17 (26%) | | |
| Cured after TVT | 5 (29%) | | |
| **Sexual function** | | | |
| Sexual active (yes) | 31 (48%) | | |
| Pain (yes)* | 9 (14%) | | |
| Other problems (yes)* | 23 (74%) | | |
| Bothering problems (yes)* | 19 (61%) | | |

***Table 6*** *Demographic data and baseline characteristics of all the 65 included women (new). Values are expressed as either numbers (percent) or means (standard deviation, SD) and median (interquartile range, IQR).OASIS=obstetric anal sphincter injury. EAUS=endoanal ultrasonography. EQ-5D=European Quality of Life-5 Dimensions. ICIQ-UI SF= International Consultation on Incontinence Questionnaire- Urinary Incontinence Short Form. * Only assessed in sexually active.*

*Table 7*

| | **Responders (n=56)** | **Non-responders (n=7)** | **P-value** |
|---|---|---|---|
| **Age, years** | 61 (50-67) | 43 (41-67) | 0.2 |
| **Menopausal status** | | | **0.03** |
| Premenopausal | 15 (27%) | 5 (71%) | |
| Postmenopausal | 41 (73%) | 2 (29%) | |
| **Body mass index, kg/m$^2$** | 27 (24-31) | 24 (22-25) | **0.007** |
| **Obstetric history** | | | |
| Vaginal deliveries | 2.0 (2-3) | 2.0 (1-2) | 0.09 |
| Instrumentation | 16 (29%) | 1 (14%) | 0.7 |
| Degree of OASIS | | | 0.4 |
| 3rd degree rupture | 21 (38 %) | 4 (57%) | |
| 4th degree rupture | 35 (62%) | 3 (43 %) | |
| **EAUS defect score (0-7)** | 2.0 (1-4) | 3.0 (1-4) | 0.4 |
| **Previous secondary sphincter repair** | 6 | 2 | 0.2 |
| **Previous anorectal surgery** | 14 (25%) | 3 (43%) | 0.09 |
| **Previous gynaecological surgery including for urinary incontinence** | 23 (41%) | 2 (29%) | 0.1 |
| **St. Mark's score (0-24)** | 18.0 (15.3-20.0) | 15.0 (12-16) | **0.004** |
| **Duration of FI** | | | 0.4 |
| 1-10 years | 30 (54%) | 5 (71%) | |
| More than 10 years | 26 (46%) | 2 (29%) | |
| **Rockwood quality of life score** | | | |
| Lifestyle (0-4) | 2.6 (1.9-3.2) | 3.0 (2.1-3.6) | 0.3 |
| Coping/behaviour (0-4) | 1.6 (1.2-2.1) | 1.9 (1.6-2.4) | 0.1 |
| Depression (0-4) | 3.0 (2.1-3.8) | 3.2 (2.4-3.6) | 0.6 |
| Embarrassment (0-4) | 1.7 (1.3-2.0) | 2.3 (1.3-2.7) | 0.3 |
| **EQ-5D™** | | | |
| General health (VAS scale 0-100) | 63 (50-78) | 90 (54-90) | 0.1 |
| **Urinary Incontinence** | 44 (79%) | 3 (43%) | 0.06 |
| Urge urinary Incontinence | 36 (97%) | 1 (14%) | **0.04** |
| ICIQ-UI SF score (0-21) | 8 (3.3-15.8) | 0 (0-9) | 0.07 |

***Table** 7 Demographic data and baseline characteristics of responders (≥50% reduction in faecal incontinence episodes) compared with non-responders (<50% improvement in faecal incontinence episodes) during PNE (paper I). Values are expressed as either numbers (percent) or median (interquartile range). OASIS=obstetric anal sphincter injury. EAUS=endoanal ultrasonography. EQ-5D=European Quality of Life-5 Dimensions. ICIQ-UI SF= International Consultation on Incontinence Questionnaire- Urinary Incontinence Short Form.*

***Table 10***

| *Group* | *Baseline* | *6 months* | *Change from baseline to 6 months* | *Difference in change from baseline to 6 months between the groups* | | | |
|---|---|---|---|---|---|---|---|
| | | | | *B, Unadjusted* | ***P-value*** | *B, adjusted*[*] | ***P-value*** |
| ***Faecal incontinence*** | | | | | | | |
| *St Mark's incontinence score (0-24)* | | | | | | | |
| *SNM* | *19.0 (2.5)* | *7.7 (5.5)* | *11.2 (5.3)* | *8.93 (6.14-11.7)* | *<0.001* | *7.52 (4.67-10.4)* | *<0.001* |
| *Permacol®* | *16.8 (3.4)* | *14.3 (4.5)* | *2.3 (5.0)* | | | | |
| ***Faecal incontinence quality of life scale (FIQL)*** | | | | | | | |
| *Lifestyle (0-4)* | | | | | | | |
| *SNM* | *2.40 (0.72)* | *3.45 (0.62)* | *1.05 (0.84)* | *0.90 (0.50-1.30)* | ***<0.001*** | *0.76 (0.41-1.10)* | ***<0.001*** |
| *Permacol®* | *2.63 (0.85)* | *2.83 (0.83)* | *0.15 (0.61)* | | | | |
| *Coping (0-4)* | | | | | | | |
| *SNM* | *1.54 (0.48)* | *2.79(0.79)* | *1.25 (0.84),* | *1.05 (0.62-1.47)* | ***<0.001*** | *0.94 (0.53-1.34)* | ***<0.001*** |
| *Permacol®* | *1.76 (0.59)* | *1.9 (0.73)* | *0.20 (0.72)* | | | | |
| *Depression (0-4)* | | | | | | | |
| *SNM* | *2.86 (0.87)* | *3.51(0.69)* | *0.65 (0.66)* | *0.52 (0.16-0.87)* | ***0.005*** | *0.53 (0.18-0.53)* | ***0.001*** |
| *Permacol®* | *2.83 (0.95)* | *2.97 (0.94)* | *0.14 (0.64)* | | | | |
| *Embarrassment (0-4)* | | | | | | | |
| *SNM* | *1.72 (0.64)* | *3.03(0.78)* | *1.28 (0.84)* | *0.95 (0.50-1.40)* | ***<0.001*** | *0.94 (0.49-1.38)* | ***<0.001*** |
| *Permacol®* | *1.80 (0.55)* | *2.14(0.86)* | *0.36 (0.77)* | | | | |
| ***EQ-5D*** | | | | | | | |
| *EQ-5D VAS scale (0-100)* | | | | | | | |
| *SNM* | *57.7 (19.5)* | *68.8(18.5)* | *11.1 (21.9)* | *8.4 (-2.4-19.3)* | *0.12* | *5.20 (-4.52-14.9)* | *0.29* |
| *Permacol®* | *65.2 (20.9)* | *67.2 (22.8)* | *2.7 (17.8)* | | | | |
| *EQ-5D index (-0.594 –1)* | | | | | | | |
| *SNM* | *0.68 (0.20)* | *0.74 (0.20)* | *0.059 (0.20)* | *0.031 (-0.073-0.14)* | *0.55* | *0.011 (-0.074-0.095)* | *0.80* |
| *Permacol®* | *0.75 (0.18)* | *0.78 (0.14)* | *0.028 (0.19)* | | | | |
| ***Urinary incontinence*** | | | | | | | |
| *ICIQ-UI SF score (0-21)* | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *SNM* | *11.3(6.45)* | *6.1 (6.12)* | *5.3 (5.8)* | *5.0x (1.97-8.02)* | ***0.002*** | *3.04 (0.19-5.89)* | ***0.037*** |
| *Permacol®* | *6.9 (6.34)* | *6.4 (6.23)* | *0.27 (5.4)* | | | | |

***Table 10*** *Differences between the SNM group (n=30) and Permacol® group (n=26) regarding the changes in the primary and secondary outcomes from baseline to 6 months*

*Values are mean (standard deviation). Difference in change (B) is reported as the mean (95% confidence interval) and was calculated with linear regression models, both unadjusted and *adjusted for baseline values. St Mark's incontinence score ranged from 0 (continent) to 24 (complete incontinence). FIQL= faecal incontinence quality of life. Its score ranged from 0 (worst) to 4 (best). Eq-5D= Euroqual 5-dimension. Eq-5D™ VAS ranged from 0 (worst) to 100 (best), and the index ranged from -0.594 (worst) to 1 (best). ICIQ-UI SF= International Consultation on Incontinence Questionnaire Urinary Incontinence Short Form. It ranged from 0 (continent) to 21 (complete incontinence).*

***Table 11***

| | *Baseline* | *12 months* | *Change (95% CI)* | *p-value* |
|---|---|---|---|---|
| ***Urinary incontinence*** | | | | |
| *International Consultation on Incontinence Questionnaire Urinary Incontinence Short Form (ICIQ-UI-SF) score 0 (best) to 21 (worst)* | | | | |
| *Mean (SD)* | *12.4 (5.1)* | *6.5 (5.8)* | *-5.8 (3.7-8.0)* | *<0.0001* |
| *Median (IQR)* | *13.0 (8.0-17.5)* | *8.0 (0-11.0)* | *-* | *<0.0001* |
| ***Faecal incontinence*** | | | | |
| *St Mark's score 0 (best) to 24 (worst)* | | | | |
| *Mean (SD)* | *17.8 (2.64)* | *7.1 (5.3)* | *-10.6 (8.6-12.7)* | *<0.0001* |
| *Median (IQR)* | *18.0 (15.0-19.5)* | *6.0 (3.0-11.0)* | *-* | *<0.0001* |
| ***Quality of life*** | | | | |
| *EQ-5D Vas scale 0 (worst) to 100 (best)* | | | | |
| *Mean (SD)* | *59 (20.4)* | *73 (17.8)* | *15.2 (5.6-24.9)* | *0.003* |
| *Median (IQR)* | *60 (48-75)* | *75 (70-82)* | *-* | *0.008* |
| *EQ-5D index -0.594 (worst) to 1 (best)* | | | | |
| *Mean (SD)* | *0.68 (0.20)* | *0.73 (0.21)* | *0.047(-0.04-0.13)* | *0.26* |
| *Median (IQR)* | *0.76 (0.47-0.82)* | *0.82(0.57-0.89)* | *-* | *0.16* |
| *Urinary incontinence burden 0 (best) to 10 (worst)* | | | | |
| *Mean (SD)* | *6.2 (3.3)* | *3.3 (3.4)* | *-2.9 (1.6-4.2)* | *<0.0001* |
| *Median (IQR)* | *7.0 (3.0-9.0)* | *3.0 (0-5.5)* | *-* | *<0.0001* |
| *Rockwood faecal incontinence quality of life scale (FIQL) 0 (worst) to 4 (best)* | | | | |
| *Lifestyle (0-4)* | | | | |
| *Mean (SD)* | *2.38 (0.76)* | *3.44 (0.62)* | *1.06 (0.71-1.41)* | *<0.0001* |
| *Median (IQR)* | *2.35 (1.78-2.81)* | *3.55(3.08-3.90)* | *-* | *<0.0001* |
| *Coping (0-4)* | | | | |
| *Mean (SD)* | *1.57 (0.47)* | *2.79 (0.78)* | *1.22 (0.89-1.55)* | *<0.0001* |
| *Median (IQR)* | *1.56 (1.11-1.92)* | *2.79 (2.40-3.4)* | *-* | *<0.0001* |
| *Depression (0-4)* | | | | |
| *Mean (SD)* | *2.89 (0.90)* | *3.55 (0.79)* | *0.67 (0.38-0.95)* | *<0.0001* |
| *Median (IQR)* | *3.0 (2.25-3.63)* | *4.0 (3.07-4.17)* | *-* | *<0.0001* |
| *Embarrassment (0-4)* | | | | |
| *Mean (SD)* | *1.77 (0.67)* | *3.03 (0.99)* | *1.26 (0.89-1.62)* | *<0.0001* |
| *Median (IQR)* | *1.67 (1.33-2.08)* | *3.33 (2.0-3.75)* | *-* | *<0.0001* |

***Table 11*** *Primary and secondary outcomes from baseline to 12 months (Paper III). Mean (SD), Median (IQR), Changes (95% CI)*

# KISS-studien 2012-2014 St. Mark's score

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VI BRYR OSS · SAMMEN TAR VI ANSVAR
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**Pasientdata (ID kode)** **(må fylles ut)**

Initialer ☐☐☐ Fødselsdato ☐☐☐☐☐☐

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Studienummer ☐☐☐

Baseline ☐ 3mnd ☐ 6 mnd ☐ 12 mnd ☐ Kontroll (ekstra) ☐

**ST.MARKS'S SCORE** Dato ☐☐.☐☐.☐☐☐☐

| | Aldri | Sjelden | Av og til | Ukentlig | Daglig |
|---|---|---|---|---|---|
| Lekkasje av fast avføring | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |
| Lekkasje av flytende avføring | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |
| Lekkasje av luft | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |
| Endring av livsstil | ☐ 0 | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 |

| | Nei | Ja |
|---|---|---|
| Behov for å bruke bind eller propp pga lekkasje av avføring | ☐ 0 | ☐ 2 |
| Bruk av forstoppelsesmedikamenter | ☐ 0 | ☐ 2 |
| Manglende evne til å utsette avføring i 15 minutter | ☐ 0 | ☐ 4 |

Aldri: Ingen tilfeller de siste fire ukene;
Sjelden: 1 tilfelle de siste fire ukene;
Av og til: > 1 tilfelle de siste fire ukene, men < 1 tilfelle i uka;
Ukentlig: 1 eller flere tilfeller i uka, men < 1 tilfelle per dag;
Daglig: 1 eller flere tilfeller pr dag

Legg sammen resultatet fra hver rad: minimumssum = 0 = perfekt konsistens;
maksimumssum = 24 = helt inkontinent.

St Mark's sum ☐☐

54024

# KISS-studien 2012-2014 ICIQ-UI

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Studienummer ☐☐☐ Baseline ☐ 3 mnd ☐ 6 mnd ☐ 12 mnd ☐ Kontroll (ekstra) ☐

**ICIQ-UI** Dato ☐☐.☐☐.☐☐☐☐

| 1. Hvor ofte lekker du urin? (Sett ett kryss) | 2. Hvor mye urin lekker du vanligvis (enten du bruker beskyttelse eller ikke)? (Sett ett kryss) |
|---|---|
| ☐ 0 Aldri | ☐ 0 Ikke noe |
| ☐ 1 Omtrent en gang i uken eller sjeldnere | ☐ 2 En liten mengde |
| ☐ 2 2 - 3 ganger i uken | ☐ 4 En moderat mengde |
| ☐ 3 Ca. 1 gang per dag | ☐ 6 En stor mengde |
| ☐ 4 Flere ganger per dag | |
| ☐ 5 Hele tiden | |

3. Hvor mye påvirker urinlekkasjen ditt hverdagsliv?

Vær vennlig, sett en ring rundt et tall mellom 0 (ikke i det hele tatt) og 10 (mye)

0 1 2 3 4 5 6 7 8 9 10

ikke i det hele tatt svært mye

ICI-Q sum 1 + 2 + 3 ☐☐

4. Når lekker du urin (vennligst kryss av alt som passer for deg)

- ☐ Aldri, jeg lekker ikke urin
- ☐ Lekker før jeg når toalettet
- ☐ Lekker når jeg hoster eller nyser
- ☐ Lekker når jeg sover
- ☐ Lekker når jeg er fysisk aktiv/trimmer
- ☐ Lekker når jeg er ferdig med å late vannet og har tatt på meg klærne
- ☐ Lekker uten noen opplagt grunn
- ☐ Lekker hele tiden

# KISS-studien 2012-2014 Seksualfunksjon

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Studienummer ☐☐☐ Baseline ☐ 3 mnd ☐ 6 mnd ☐ 12 mnd ☐ Kontroll (ekstra) ☐

**SEKSUALFUNKSJON** Dato ☐☐.☐☐.☐☐☐☐

1. Er du seksualt aktiv? (Sett ett kryss)

☐ Ja

☐ Nei

Hvis nei, angi grunn: ☐

2. Har du smerter ved samleie? (Sett ett kryss)

☐ Nei

☐ Ja

3. Har du noen andre problemer med sex? (Sett ett kryss)

☐ Nei

☐ Ja

Hvis ja, angi hvilke problemer: ☐

4. Er noen av dine seksuelle problemer plagsomme? (Sett ett kryss)

☐ Nei

☐ Ja

I hvilken grad opplever du problemene som plagsomme?
*Vær vennlig, sett en ring rundt et tall mellom 0 (ikke i det hele tatt) og 10 (mye)*

0 1 2 3 4 5 6 7 8 9 10

ikke i det hele tatt svært mye

41495

# KISS-studien 2012-2014 FIQL

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Studienummer ☐☐☐ Baseline ☐ 3 mnd ☐ 6 mnd ☐ 12 mnd ☐ Kontroll (ekstra) ☐

## BESKRIVELSE AV GENERELL HELSETILSTAND (FIQL)

Dato ☐☐.☐☐.☐☐☐☐

**Spørsmål 1:** Generelt vil du si at din helse er:

☐ 1 Utmerket ☐ 2 Veldig god ☐ 3 God ☐ 4 Nokså god ☐ 5 Dårlig

**Spørsmål 2:** For hvert av punktene nedenfor, vennligst angi hvor ofte du bekymrer deg for temaet på grunn av uhell med lekkasje fra endretarmen.
(Hvis det er en bekymring på grunn av andre årsaker, sett kryss i boksen Ikke relevant.)

| Spørsmål 2: På grunn av uhell med lekkasje fra endetarmen | Stort sett alltid | En del | Av og til | Aldri | Ikke relevant |
|---|---|---|---|---|---|
| a. Jeg er redd for å gå ut | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ |
| b. Jeg unngår å besøke venner | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ |
| c. Jeg unngår å overnatte hjemmefra | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ |
| d. Det er vanskelig for meg å gå ut og gjøre ting som å gå på kino eller gå i kirken | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ |
| e. Jeg spiser mindre før jeg går ut | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ |
| f. Når jeg er hjemmefra, prøver jeg å holde meg i nærheten av et toalett så mye som mulig | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ |
| g. Det er viktig at jeg planlegger timeplanen min (daglige aktiviteter) rundt avføringsmønsteret mitt | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ |
| h. Jeg unngår å reise | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ |
| i. Jeg bekymrer meg for å ikke nå frem til toalettet i tide | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ |
| j. Jeg føler at jeg ikke har noen kontroll over avføringen min | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ |
| k. Jeg kan ikke holde meg lenge nok til at jeg rekker frem til toalettet i tide | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ |
| l. Jeg lekker avføring uten at jeg merker det | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ |
| m. Jeg prøver å unngå lekkasjeepisoder ved å oppholde meg nært et toalett | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ |

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Studienummer ☐☐☐ ☐ Baseline ☐ 6 mnd ☐ 12 mnd ☐ Kontroll (ekstra)

**Spørsmål 3:** På grunn av uhell med lekkasje fra endetarmen, vennligst kryss av for i hvilken grad du er ENIG eller UENIG med hvert enkelt av spørsmålene under.
(Hvis det er en bekymring på grunn av andre årsaker, sett kryss i boksen Ikke relevant.)

| Spørsmål 3: På grunn av uhell med lekkasje fra endetarmen | Enig | Litt enig | Litt uenig | Uenig | Ikke relevant |
|---|---|---|---|---|---|
| a. Jeg skammer meg | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ |
| b. Jeg kan ikke gjøre mange av de tingene jeg har lyst til å gjøre | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ |
| c. Jeg bekymrer meg for lekkasjeepisoder | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ |
| d. Jeg føler meg deprimert | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ |
| e. Jeg bekymrer meg for at andre skal kjenne avføringslukt fra meg | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ |
| f. Jeg føler meg ikke som en frisk person | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ |
| g. Jeg har mindre glede av livet | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ |
| h. Jeg har sjeldnere sex enn det jeg har lyst til å ha | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ |
| i. Jeg føler meg annerleders enn andre mennesker | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ |
| j. Muligheten for lekkasje fra endretarmen er alltid i tankene mine | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ |
| k. Jeg er redd for å ha sex | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ |
| l. Jeg unngår å reise med fly eller tog | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ |
| m. Jeg unngår å gå ut og spise på resturant | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ |
| n. Hver gang jeg er på et nytt sted, sørger jeg alltid for å finne ut hvor toalettene er | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ |

**Spørsmål 4:** Har du i løpet av den siste måneden følt deg så nedfor eller hatt så mange problemer at du har tenkt at ingenting har noen hensikt lenger?

☐ 1 Ja, svært mye - så mye at jeg nesten har gitt opp
☐ 2 Ja, veldig
☐ 3 Ganske mye
☐ 4 Av og til - nok til at det bekymrer meg
☐ 5 Litt
☐ 6 Ikke i det hele tatt

62413

***Faecal incontinence quality of life scale***

# KISS-studien 2012-2014 EQ-5D

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Studienummer ☐☐☐ Baseline ☐ 3 mnd ☐ 6 mnd ☐ 12 mnd ☐ Kontroll (ekstra) ☐

## BESKRIVELSE AV GENERELL HELSETILSTAND (EQ-5D)

Dato ☐☐.☐☐.☐☐☐☐

Vis hvilke utsagn som passer best på din helsetilstand i dag ved å sette kun *ett kryss* i en av rutene for hvert punkt nedenfor.

### 1. Gange

- ☐ Jeg har ingen problemer med å gå omkring
- ☐ Jeg har litt problemer med å gå omkring
- ☐ Jeg er sengeliggende

### 2. Personlig stell

- ☐ Jeg har ingen problemer med personlig stell
- ☐ Jeg har litt problemer med å vaske meg eller kle meg
- ☐ Jeg er ute av stand til å vaske meg eller kle meg

### 3. Vanlige gjøremål (f.eks arbeid, studier, husarbeid, familie- eller fritidsaktiviteter)

- ☐ Jeg har ingen problemer med å utføre mine vanlige gjøremål
- ☐ Jeg har litt problemer med å utføre mine vanlige gjøremål
- ☐ Jeg er ute av stand til å utføre mine vanlige gjøremål

### 4. Smerte og ubehag

- ☐ Jeg har hverken smerte eller ubehag
- ☐ Jeg har moderat smerte eller ubehag
- ☐ Jeg har sterk smerte eller ubehag

### 5. Angst og depresjon

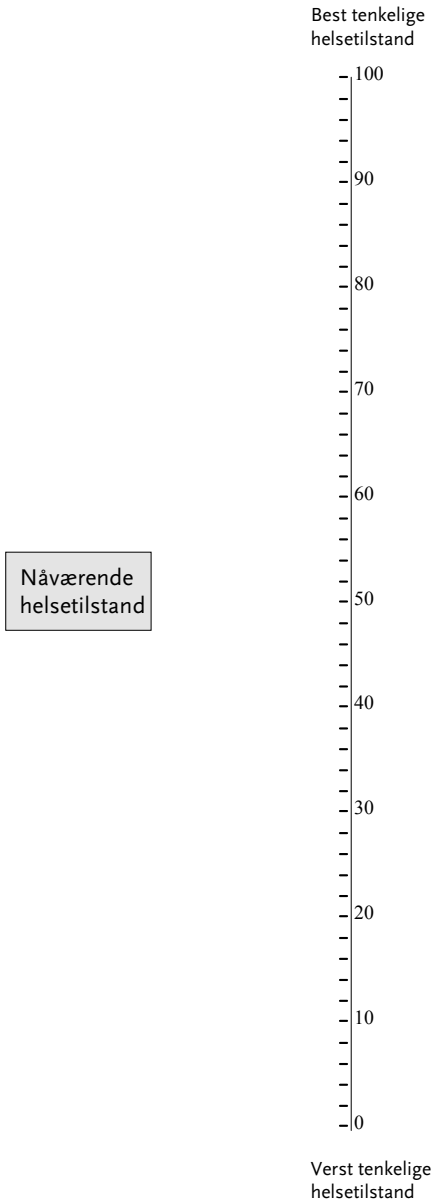
- ☐ Jeg er hverken engstelig eller deprimert
- ☐ Jeg er noe engstelig eller deprimert
- ☐ Jeg er svært engstelig eller deprimert

Sykehuset Østfold (100) ☐ Ahus (200) ☐ Haukeland (300) ☐ St. Olav (400) ☐ UNN (500) ☐ Hvidovre (600) ☐

Studienummer ☐☐☐ Baseline ☐ 3 mnd ☐ 6 mnd ☐ 12 mnd ☐ Kontroll (ekstra) ☐

## Helsetilstand

For at du skal kunne vise oss hvor god eller dårlig din helsetilstand er, har vi laget en skala (nesten som et termometer), hvor den beste helsetilstanden du kan tenke deg er markert med 100 og den dårligste med 0.
Vi ber om at du viser din helsetilstand ved å trekke ei linje fra boksen nedenfor til det punkt på skalaen som passer best med din helsetilstand.




40730



***EQ-5D-3L***