Refining and improving the assessment and treatment of faecal incontinence

A thesis by
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To
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Submitted for the degree of
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To my wife Chiara

Declaration

I hereby acknowledge that this thesis and the research it describes are the product of my own work, and that where it has been the result of collaboration with others, this is fully described. Quotations from the work of other researchers are fully acknowledged in accordance with standard referencing practice.

Cosimo Alex Leo

Copyright declaration

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Abstract

Faecal incontinence (FI) is a common symptom. There are a variety of invasive treatments available, however, the benign nature of this problem and the varying degrees of severity, mean that conservative management is usually pursued first. The aims of this thesis were to investigate: the current practice of continence advisors who deliver conservative management in the community in the UK; assess and evaluate a new portable manometric device (THD® Anopress); investigate a new first line treatment for FI (Renew™) and compare this to another well-established non-invasive treatment (PTNS); report the long-term effectiveness of SNM; and, describe the short term outcome of the newer Sphinkeeper procedure. Results of this thesis lead to the conclusion that continence advisors are an important part of the management of FI in the community and that while they are able to utilise many of the current treatments, there is room for improvement. Normal range values for the new portable manometric device Anopress have been reported for the first time. It has been demonstrated that Anopress device appears able to detect anal sphincter dysfunction in those with symptomatic FI, and most importantly, Anopress measurements correlate strongly with water-perfused manometry. Results reported by this thesis also demonstrated that the Renew device is safe, well tolerated and an effective non-invasive treatment for passive FI. The randomized controlled trial suggests that both the Renew device and PTNS are effective treatments for FI, although Renew inserts may be more effective than PTNS. SNS was confirmed as an effective treatment for FI even in the long term with a consistent improvement of validated FI scores for approximately 60% of all patients reviewed at 11 years post implantation. Sphinkeeper was also demonstrated to be a safe and feasible alternative procedure for FI.

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Abbreviations

FI – Faecal Incontinence

CA – Continence Advisor

SM – Social Media

PTNS – Percutaneous Tibial Nerve Stimulation

PNE – Peripheral Nerve Evaluation

SNS – Sacral Nerve Stimulation

SNM – Sacral Neuromodulation

ARP – Anorectal Physiology

WPM - Water Perfused Manometry

EAUSS – Endo Anal Ultra Sound Scan

MRI – Magnetic Resonance Imaging

CT – Computational Tomography

DTI – Diffusion Tensor Imaging

DGP – Dynamic Graciloplasty

Publications arising from this thesis

Peer reviewed journals:

- *Randomized pilot study anal inserts versus Percutaneous Tibial Nerve Stimulation (PTNS) in patients with faecal incontinence. Leo CA, Thomas GP, Hodgkinson JD, Leeuwenburgh M, Bradshaw E, Warusavitarne J, Murphy J, Vaizey CJ. DCR. 2020 Dec 01.* Online ahead of print.

- *Long-term outcome of sacral nerve stimulation for faecal incontinence. Leo CA, Thomas GP, Bradshaw E, Karki S, Hodkinson JD, Murphy J & Vaizey CJ. Colorectal Dis. 2020 Sep 11. Online ahead of print.*

- *Initial experience with SphinKeeper™ intersphincteric implants for faecal incontinence in the United Kingdom: a two-centre retrospective clinical audit. Leo CA, Leeuwenburgh M, Orlando A, Corr A, Scott M, Murphy J, Knowles CH[5], Vaizey CJ, Giordano P. Colorectal Dis. 2020 July 19. Online ahead of print.*

- *Comparison of high-resolution water perfused anorectal manometry with the THD® Anopress anal manometry: a prospective observational study. Leo CA, Cavazzoni E, Leeuwenburgh MMN, Thomas GP, Dennis A, Bassett P, Hodgkinson JD, Warusavitarne J, Murphy J, Vaizey CJ. Colorectal Dis. 2020 Jan 28. Online ahead of print.*

- *Evaluation of the Portable THD® Anopress Device in Patients with Faecal Incontinence. Leo CA, Murphy J, Cavazzoni E, Thomas GP, Shaikh S, Hodgkinson JD, Warusavitarne J and Vaizey CJ. J Gastrointest Dig Syst 2018, Vol 8(6): 582.*

- *The Renew® Anal Insert for Passive Faecal Incontinence: a retrospective audit of our use of a novel device. Leo CA, Thomas GP, Hodgkinson JD, Segal JP, Maeda Y, Murphy J, Vaizey CJ. Colorectal Dis. 2019 Jun;21(6):684-688.*

- *Evaluation of 153 asymptomatic subjects using the Anopress portable anal manometry device. Leo CA, Cavazzoni E, Thomas GP, Hodgkinson JD, Murphy J & Vaizey CJ. Journal of Neurogastroenterology and motility. 2018 Jul 30;24(3):431-436.*

- *Current practice of continence advisors in managing faecal incontinence in the United Kingdom: results of an online survey. Leo CA, Maeda Y, Collins B, Thomas GP, Hodgkinson JD, Murphy J, Vaizey CJ. 2017 Sep;19(9):O339-O344.*

Posters and published abstracts:

- *Randomized Pilot Study of the Renew™ Anal Insert Versus Percutaneous Tibial Nerve Stimulation (PTNS) in Patients Suffering from Faecal Incontinence. Leo CA et al. ASCRS Boston (US) 2020; quick shot of distinction. Abstract published in DC&R Journal. 2020; Suppl. QS453.*

- *Comparing Water Perfused Anorectal Manometry with the THD® Anopress: A Prospective Observational Study. Leo CA et al. ASCRS Boston (US) 2020; abstract published in DC&R Journal. 2020; Suppl. P1303.*

- *Visualisation and assessment of sacral nerve roots using diffusion tensor imaging. Vaizey CJ et al. ESCP Vienna (A) 2019. Abstract published in Colorectal Disease Journal. 2019; Vol. 21, Suppl. 3. P391.*

- *Preliminary results of Sphincter intersphincteric self-expandable prostheses for faecal incontinence. Giordano P et al. ESCP Vienna (A) 2019. Abstract published in Colorectal Disease Journal. 2019; Vol. 21, Suppl. 3. P432.*

- *Efficacy and acceptability of the Renew anal insert in patients who have undergone restorative proctocolectomy. Clark S et al, British Society of Gastroenterology, Liverpool (UK) 2018. Abstract published in Gut Journal. 2018; Vol. 67, Suppl 1. A1 – A304.*

- *Long term outcome of Sacral Nerve Stimulation (SNS) for faecal incontinence. Leo CA et al, ESCP European Society of Coloproctology, Berlin (D) 2017. Abstract published in Colorectal Disease Journal. 2017 Sept; Vol. 17, Suppl 2. P020.*

- *Normal range values of a new bedside manometry: Anopress©. Leo CA et al, ASCRS Annual Scientific and Tripartite Meeting in Seattle, WA (US) 2017. Abstract published in DC&R Journal. 2017 June. Suppl.*

- *Current practice of continence advisors in the UK: results from an online survey. Leo CA et al, ESCP European Society of Coloproctology, Milan (I) 2016. Abstract published in Colorectal Disease Journal. 2016 Sept. Suppl.*

1 Background and introduction

1.1 Anatomy of the anorectum

The rectum and anal canal comprise the last portion of the large intestine. The rectum is located in the pelvis, begins at the level of the sacral promontory, and extends 12 to 18 cm distally. This portion of the enteric tract differs from the colon as it has the adventitial teniae bands merged to form the outer longitudinal muscle (1). The rectum has two curves along its length (Fig. 1.1):

- Sacral flexure: this extends antero-posteriorly with a concavity anteriorly following the curve of the sacrum and coccyx.
- Anorectal flexure: this extends antero-posteriorly but with a convexity anteriorly. This flexure is formed by the tone of the puborectalis muscle and is pivotal in maintaining continence.

The peritoneum covers the upper two-thirds of the rectum anteriorly, but only the upper third laterally. The reflection of the peritoneum goes caudally to approximately 6 to 8 cm above the anal verge. Finally, the lower one-third of the rectum is without peritoneal covering. The rectum is also enveloped by an endopelvic fascia named the mesorectal fascia, but is often referred to as Denonvilliers fascia on the anterior aspect of the rectum (2).

While the posterior rectal anatomic relations are similar in males and females (sacrum, coccyx, levator ani, sacral plexus), the anterior rectal anatomic relations are different between the two genders (Fig. 1.2):

- In male, the rectum has relations anteriorly with recto-vescical pouch, sigmoid colon, ileum, bladder, prostate, seminal vesicles.
- In the female, the rectum has relations anteriorly with the recto-uterine pouch, sigmoid colon, ileum, vagina and cervix.

The anal canal is the terminal portion of the intestinal tract and continuous from the rectum to the external orifice. This short segment of the intestinal tract is essential for maintaining continence. Some authors distinguish an anatomical anal canal from the surgical / functional anal canal (3,4):

- The anatomical anal canal is approximately 1.5-2 cm long and it extends from the orifice up to a demarcation line at approximately the midpoint of the anal canal, about 2 cm from the anal verge named as dentate line.
- The surgical/functional anal canal arises from the verge up to the anorectal ring. This definition of the anus will be used for the purpose of this thesis.

The anal canal is ca. 4 cm in length although many authors define a 2.5 cm to 5 cm range for the normal length of the anal canal (4,5). The anus is surrounded by two important muscles that act as two tubes, one surrounding the other, separate from each other but also integrated (Fig. 1.3):

- The inner tube is called the internal sphincter muscle and being visceral, is a smooth muscle and innervated by the autonomic nervous system; this originates from the thickened portion of the circular visceral layer of the rectum.

- The outer tube, called external sphincter muscle, is a skeletal muscle and has somatic innervation. It is divided into three sections: deep, superficial and subcutaneous portions.

Figure 1. 1: The rectal flexures. From https://teachmeanatomy.info/abdomen/gi-tract/rectum/, access on 14th February 2020.

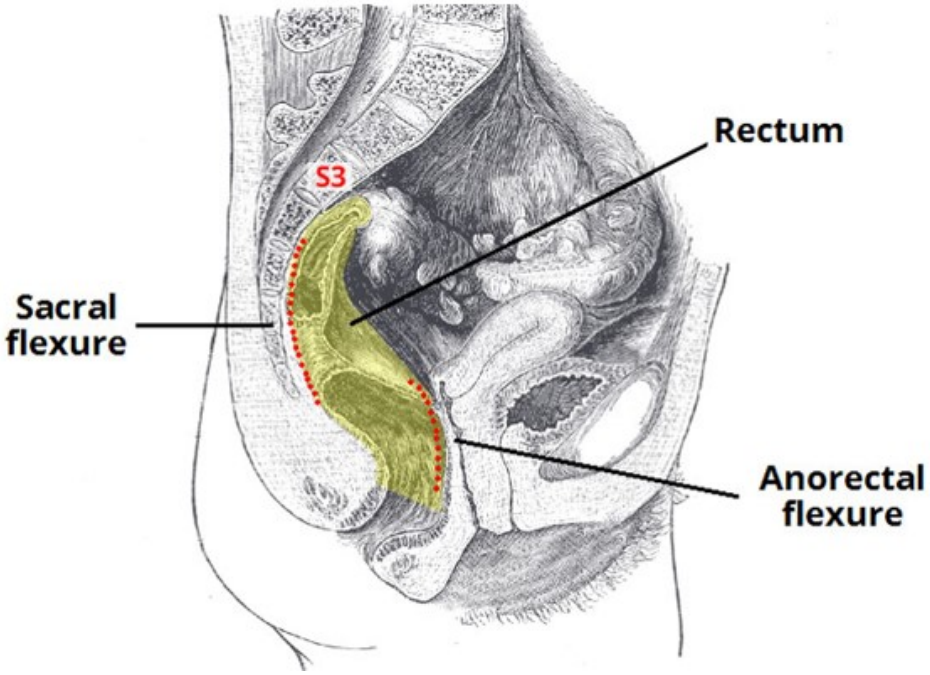
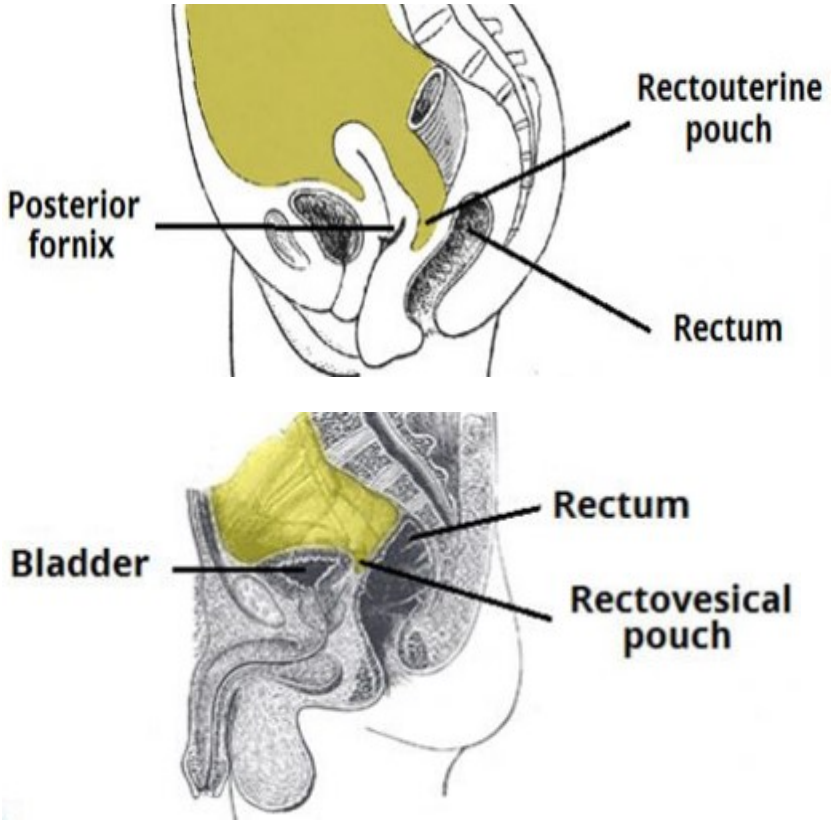


Figure 1. 2: Anatomical relations of the anorectum in female and male respectively. From https://teachmeanatomy.info/abdomen/gi-tract/rectum/, access on 14th February 2020.



Above these two important muscular structures, there is a further voluntary muscle complex known as the levator ani. This forms much of the pelvic floor (Fig. 1.4). It consists of the puborectalis muscle medially, the ileococcygeal muscles posterolaterally and the pubococcygeal muscle also posterolaterally. Together they support the viscera of the pelvic cavity and play a pivotal role in micturition and defecation.

The dentate line is visibly identifiable as the tissue takes on a pleated appearance. These longitudinal folds, of which normally there are 6 to 14, are also known as the columns of Morgagni. Between adjacent columns, there are small pockets or also known as crypts. The mucosa of the upper anal canal, above the dentate line, is lined by columnar epithelium. Below the dentate line, the anal canal is lined with squamous epithelium. The change is not abrupt as for a distance of about 1 cm above the dentate line, there is a gradual transition where columnar, transitional, or squamous epithelium may be found. The skin area below the dentate line is full of accessory skin structures such as hair, sebaceous and sweats glands. This pale, delicate, smooth, thin, and shiny stretched tissue is referred to as anoderm.

The anorectum receives its vascular supply from three main branches:

- Superior rectal artery, which is the terminal continuation of the inferior mesenteric artery.
- Middle rectal artery, which is a branch of the internal iliac artery.
- Inferior rectal artery, which is a branch of the internal pudendal artery.

Similarly, venous drainage of the rectum is via the corresponding superior, middle and inferior rectal veins. The superior rectal vein empties in the portal venous system, whilst the middle

and inferior rectal veins empty into the systemic venous system. The lymphatic drainage of the rectum is via the para-rectal lymph nodes, which drain into the inferior mesenteric nodes. Additionally, the lymph from the lower aspect of the rectum drains directly into the internal iliac lymph nodes.

The innervation of the anorectum is quite complex (Fig. 1.5). Sympathetic nerves arising from the first three lumbar segments of the spinal cord are responsible for the main innervation of the rectum. After leaving the lumbar region, they join at the preaortic plexus and extend caudally from the aortic bifurcation toward the mesenteric plexus before reaching the level of the upper rectum. It then bifurcates into the left and right branches, travelling down both sides of the pelvis before joining the parasympathetic nerve branches. The parasympathetic nerve supply originates from the caudal 3 sacral nerve roots. The fibres then descend anteriorly down to the sympathetic fibres to create the pelvic plexus, which is located lateral to the levator ani muscle. The pelvic plexus plays a pivotal role in supplying the urinary and genital organs and the rectum with both parasympathetic and sympathetic fibres. The pudendal nerves arise from S2 – S3 and S4. The nerves run in the lateral wall of the ischioanal fossa bilaterally and their branches reach into the inferior rectal, perineal, and dorsal nerves of the penis or clitoris. The anal canal also receives innervation from both sympathetic and parasympathetic fibres. Both inhibit the internal anal sphincter. The external sphincter relies on innervation from the perineal branch of the fourth sacral nerve and the inferior rectal branch of the internal pudendal nerve. The levator ani muscle is innervated by branches of the pudendal, inferior rectal, perineal, and sacral (S3 and S4) nerves. Sensation of the anal canal comes from the inferior rectal nerve, also a branch of the pudendal nerve. The epithelium of the anal canal is extensively innervated up to 2 cm proximal to the dentate line. Proximal to the dentate line, the epithelium is supplied by

the autonomic nervous system, whereas distally the lining is richly innervated by the somatic nervous system (2,3).

Figure 1. 3: Anatomy of the anus. Copyright by F.H. Netter. Atlas of Human Anatomy. Elsevier – Health Science division. Published in 2011 (3).

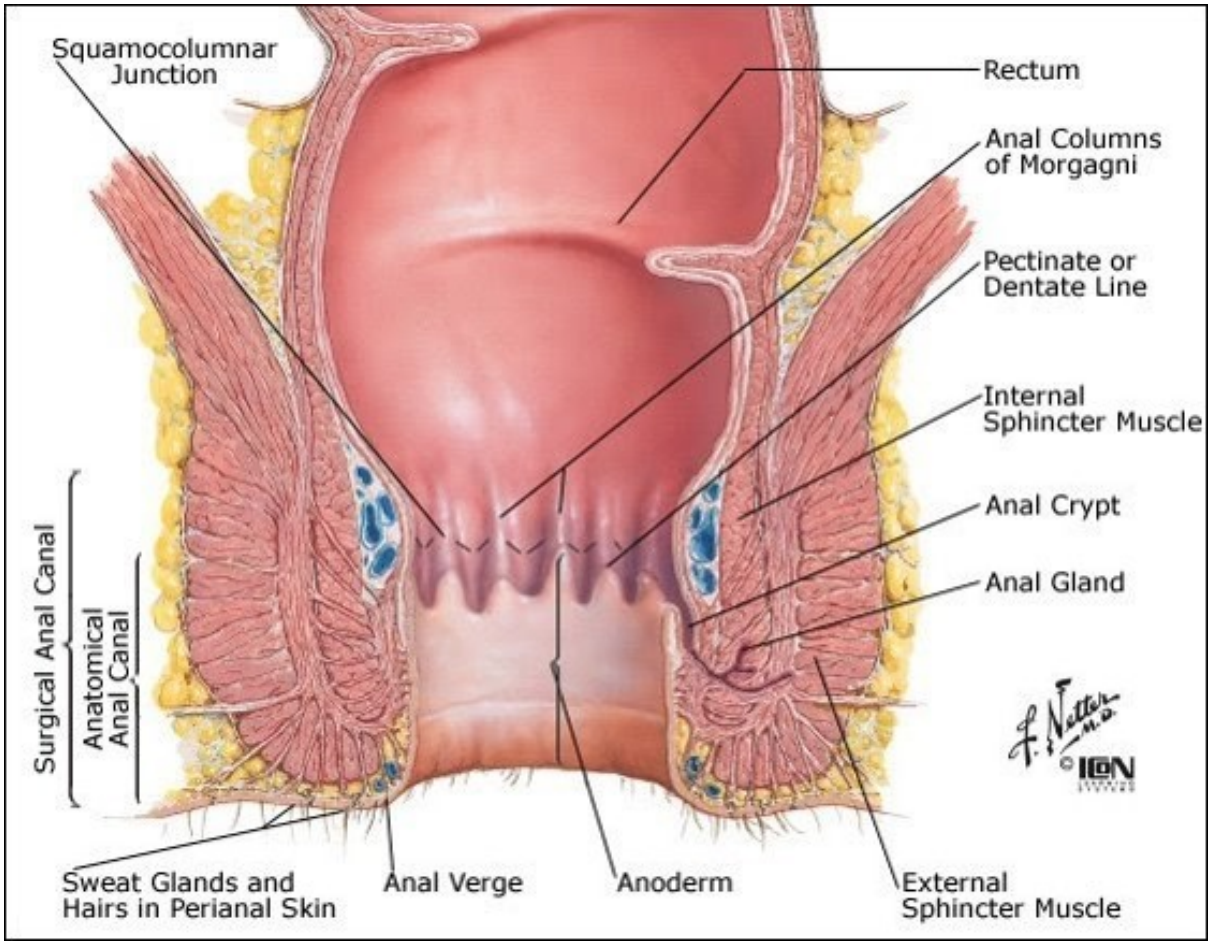


Figure 1. 4: Anatomy of the pelvic floor with particular interest to the levator ani and the pelvic diaphragm. Courtesy by Kenhub (6).

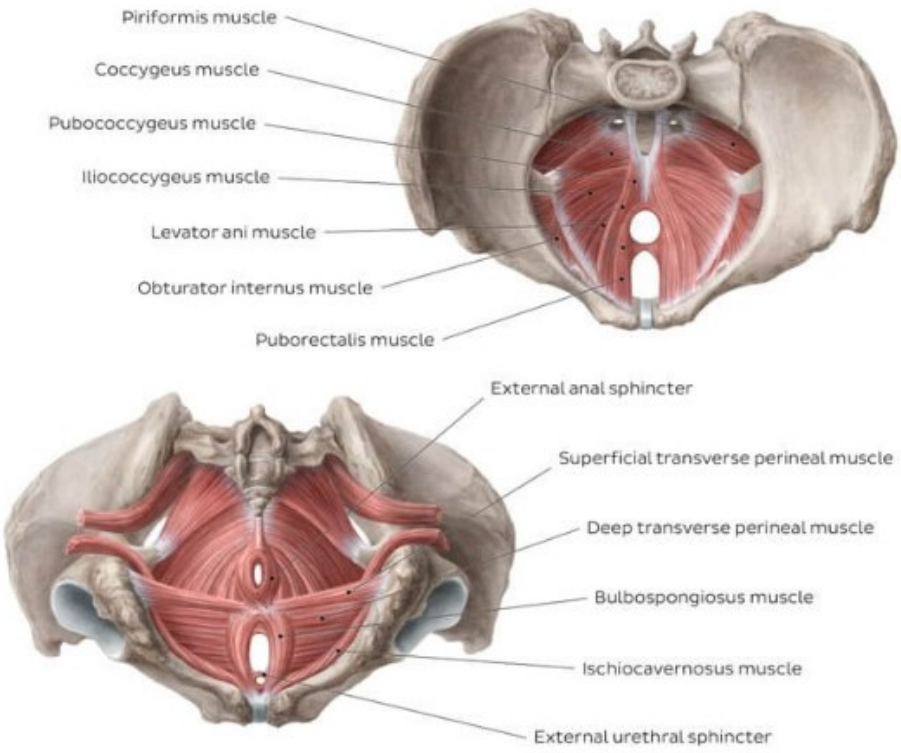
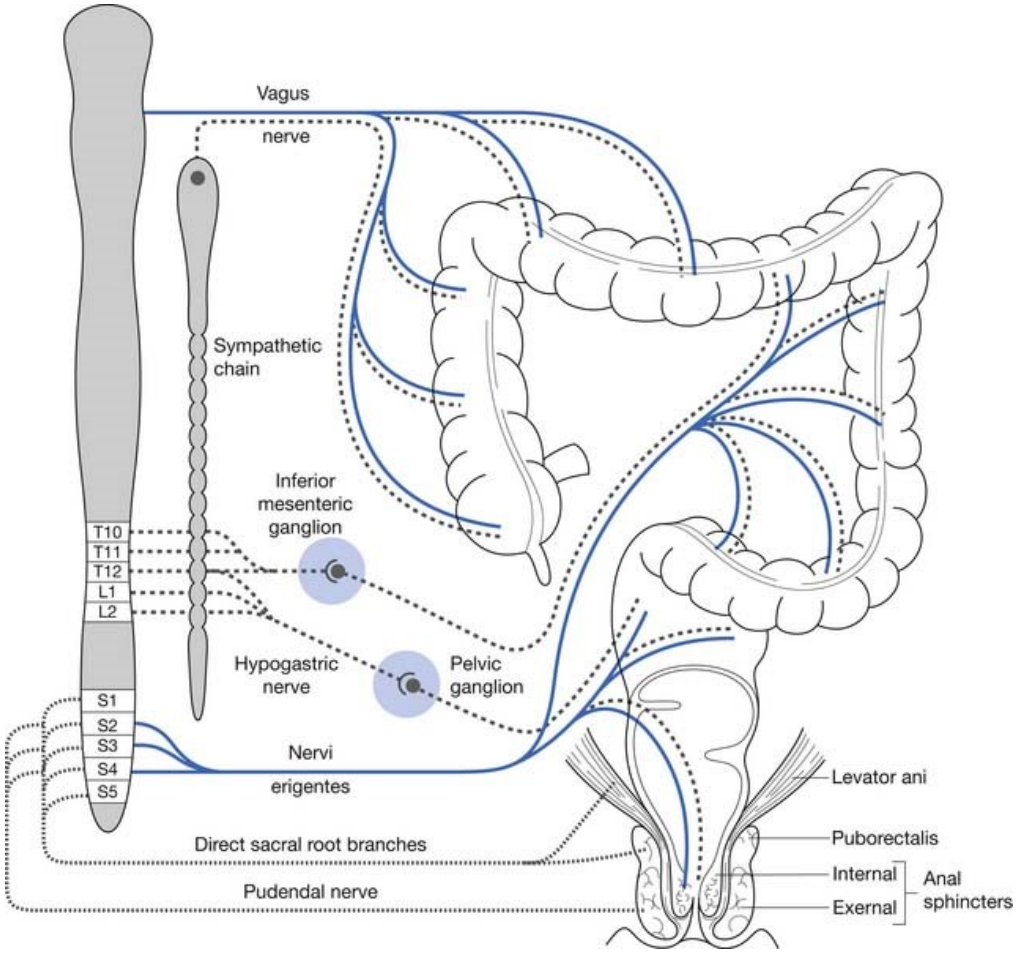


Figure 1. 5: Innervation of the colon and anorectum. From www.musculoskeletalkey.com, access on 27th March 2020.



1.2 Anorectal function

The anorectum has two main important functions: to storage faeces and to control defecation. Defecation is a very complex mechanism and involves several anatomical structures (Fig. 1.6). It occurs on an average of once or twice a day, although for some individuals this may occur every 72 hours. The process starts with a mass peristaltic movement that shifts the accumulated faeces onward from the colon to the rectum where faecal material is stored (reservoir continence). The rectum, which is normally empty, fills up with faeces and continence is maintained with the help of a sampling mechanism that allows the rectum to distinguish between the states of faecal matter: solid, liquid, or gas. The sampling mechanism in itself is an unknown process that occurs with the help of receptors located in the rectal wall and in the anal canal mucosa. When the rectum reaches a certain level of intraluminal pressure, and social conditions are favourable, the impulse to defecate occurs. The first anatomical structure involved in this process is the puborectalis muscle that anatomically forms a sling around the junction of the rectum with the anal canal maintaining a constant state of tension. This results in angulation of the lower rectum so that the lumen of the rectum and the lumen of the anal canal are not in continuity at rest. However, when defaecation stimuli occur, anorectal continuity is restored by full relaxation of the puborectalis muscle. The anorectal angle normally measures between 108° and 127° at rest, but this changes as the puborectalis muscle contracts or relaxes. Normally, the anorectal angle closes between when at rest or squeezing and opens when changing from the at rest state to defecation by c. 15°–20° (Fig. 1.7). At the same time the longitudinal muscles of the distal and pelvic colon contract. The resulting shortening of the distal colon tends to elevate the pelvic colon and obliterates the angle that it normally makes with the rectum. The straightening and shortening of the lumen facilitates the complex process of defecation. This act is also preceded by distension of the rectum to faeces

and by a voluntary effort that magnifies the visceral reflexes. Neural centres that control defecation reflexes are found in the hypothalamus of the brain, in two regions of the spinal cord, and in the ganglionic plexus of the intestine. As a result of these reflexes, and of complex voluntary and involuntary actions, the internal and the external sphincters relax allowing evacuation (4,5).

The control of the internal anal sphincter is thought to be a complex interaction between the intrinsic and extrinsic neuronal systems and myogenic neurons. The external anal sphincter also has continuous tonic activity at rest and even during sleep, which defines this muscle as unique as other striated muscles are electrically silent at rest. Also, postural changes and other increases in intra-abdominal pressure including simple actions as sneezing or coughing, increase the resting tone of the external sphincter by an anal reflex. This mechanism is modulated by the second sacral spinal segments, which allow a voluntary contraction of the muscle for 40- to 60-second periods.

Figure 1. 6: Mechanism of defecation. Image from St Mark's Hospital Academic Institute archives: Ms Carolynne J Vaizey, "Anorectal Physiology" Jan. 2016, PowerPoint presentation.

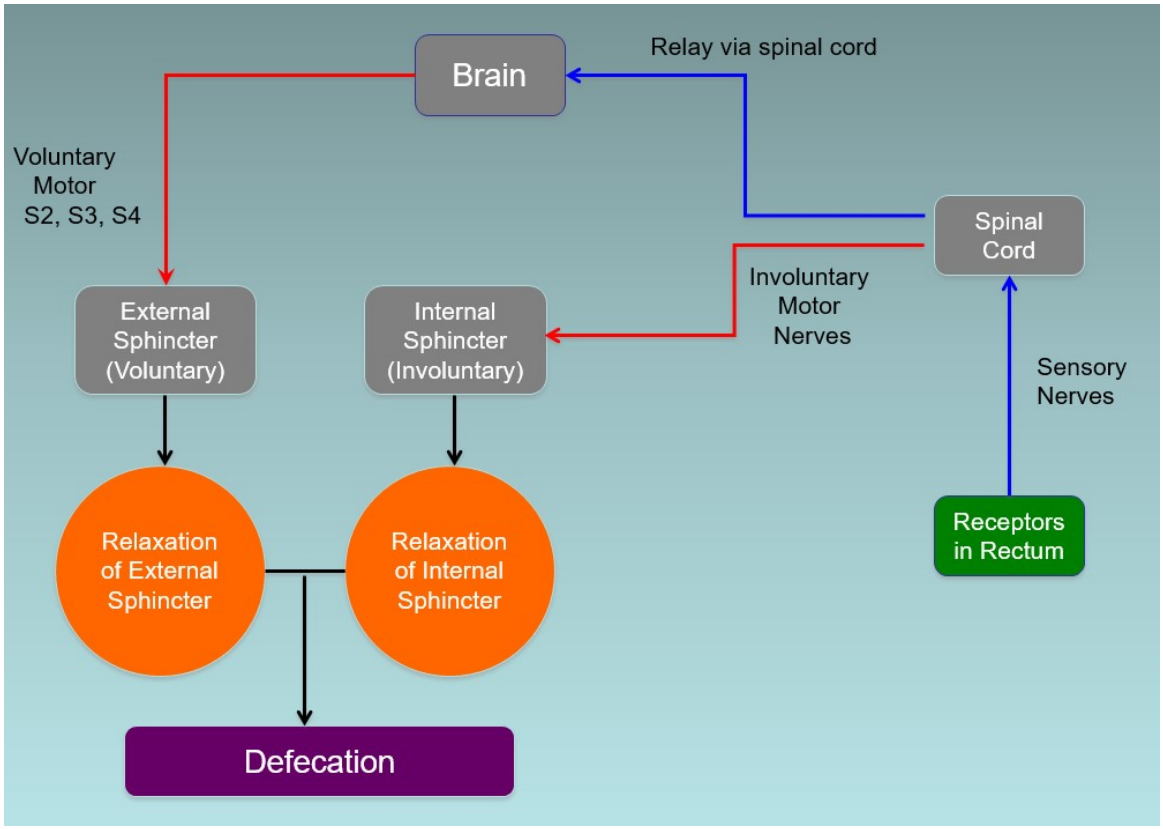
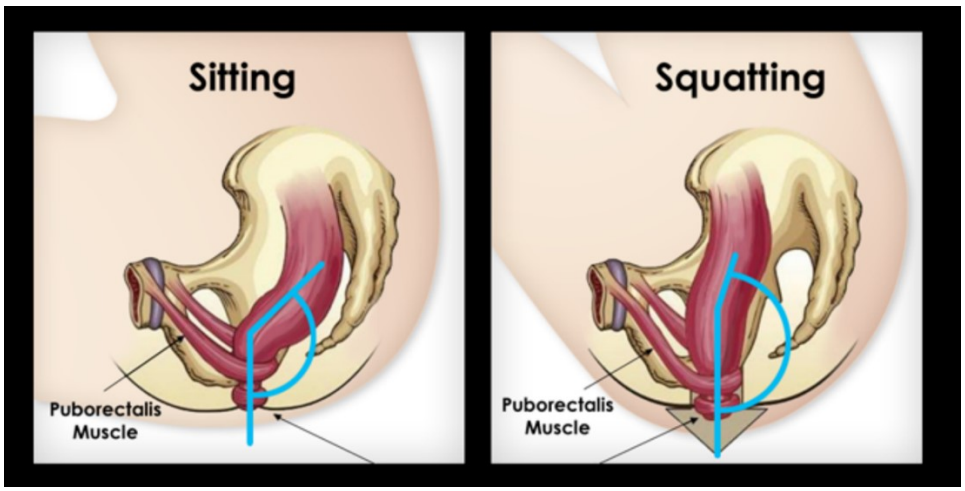


Figure 1. 7: The anorectal angle closes between at rest and squeezing and opens between rest and defecation by about 15°–20°. Image from St Mark's Hospital Academic Institute archives: Ms Carolynne J Vaizey, "Anorectal Physiology" Jan. 2016, PowerPoint presentation.



1.3 Definition and epidemiology of Faecal Incontinence

Faecal Incontinence (FI) is defined as the involuntary passage of solid or liquid faecal material including leakage of gas through the anal canal (7–9). This can be a distressing and embarrassing problem which can affect the quality of life of many people. It may lead to an overwhelming impact on self-esteem and social isolation. Incontinence is a huge problem and affects over 200 million people worldwide (10).

The true prevalence of FI is unknown, it is estimated that 2% of the general population may suffer from the inability to control bowel emptying. However, these figures may vary significantly depending on age, gender, sub-type of incontinence included in the studies and many more variables (11).

The reported prevalence of faecal incontinence can vary from 1.4% in the general population to 46% in the institutionalised elderly (12). The real prevalence of FI may be even higher than reported. Many individuals hide the problem from their families, friends and even from their doctors leading to the difficulty in ascertaining those figures. The embarrassment and the social stigma attached to this condition leads them to withdraw from their social life and may make them hesitate to seek help (13,14).

Barucha *et al* summarised the largest population-based study on the epidemiology of FI (15). This study suggested that the overall prevalence of FI ranges from 7 to 15% in the community (Fig. 1.8). However, the wide variation in prevalence may be a result of the different surveys used to collect data. Some studies suggest that FI may affect all ages and both sexes, but most authors suggest that FI more commonly affects women; however, it has also been reported that

women are keener to report their FI symptoms compared to men (16). Calculation of the true prevalence of FI is not an easy task due to these biases. FI prevalence varies in relation of how authors describe it: The International Continence Society (ICS) points out that occasional seepage could be a simple consequence of minor illness, travel or even changes in diet, therefore it is a symptom that should not be included when diagnosing FI. However, most of the published literature includes leakage in their questionnaires and their reports, therefore creating a widely varying prevalence that is determined by the definition of FI (17).

Three large systematic reviews contributed significantly to the widely stated estimates of prevalence in the literature. All included a prospective continence assessment, validated continence scores, a community-based population and appropriate outcome measures. When these three reviews were analysed together the overall prevalence of FI was stated to be 7.7% (18–20). Similar results were reported by the National Health and Nutrition Examination Survey (NHANES) in the USA, which found the prevalence of FI was 8.4% (21).

FI most commonly affects cohorts of children born with congenital anomalies of the anorectum (22). FI can occur in nearly half of this group of patients. Children without congenital abnormalities may also have FI symptoms. A Swiss cohort found complete continence occurred in 33% of children by age of 1 year, 75% by age of 2 and 97% by the age of 3 (23).

Figure 1. 8: Population based surveys of prevalence of FI. This figure demonstrates how difficult the ascertainment of FI is, Milson *et al* (17).

COUNTRY (ref)	POPULATION	N	PREVALENCE
U.K. [900]	Community Service	4844	1.90%
France [921]	All >45 years	1100	11%, 6% to faeces, 60% are women
U.S.A. [919]	Market mailing	5430	7% soiling, 0.7% to faeces
U.S.A. [901]	Wisconsin households	6959	2.2%, 63% women
Australia [918]	Household survey	3010	6.8% in men, 10.9% in women, >age 15
Germany [924]	>18 years	500	4.4%-6.7% (by health)
Australia [923]	>18 years	618	11-20% (gender M>F)
Australia [925]	>18 years	651	11.30%
New Zealand [927]	>18 years old	717	8.1% for solid and higher for gas
U.K. [928]	>40 years	10116	1.40%
U.K. [929]	Postpartum women	549	5.50%
Canada [930]	Postpartum women	949	3.1% solid, 25.5% flatus
Denmark [931]	Postpartum women	1726	8.6% in past year, 0.6% to solid stool
Nigeria [932]	Gynecology patients	3963	6.9%, 2.3% to solid stool
United Arab Emirates [933]	Women multips	450	11.3%, 5.5% to solid stool
Canada [934]	Teenage females	228	3.5% flatus, 3% FI
Czech Republic [935]	Gynecology patients	2212	5.6%, 4.4% in the community
Japan [936]	Cystectomy patients	28	60.7% post ureterosigmoidostomy
Sweden [937]	Prostate cancer	864	RR 1.3-4.5
Australia [938]	Diabetics	8657	Increased risk
Holland [939]	Women >60 years	719	4.2% to 16.9% with rising age
U.S.A. [940]	>65 years at home	328	3.7% (M >F)
Japan [941]	>65 years at home	1405	6.6-8.7% (by age).
U.S.A. [942]	>50 years	1440	11.1 – 15.2% (F > M)

1.4 Pathophysiology, aetiology and risk factors

The aetiology of FI is diverse and multifactorial. Damage to the internal or the external anal sphincter is the most common cause of this condition (11). There are several other causes including loose stool, intestinal hurry and neurological injury or disease. In most cases, a combination of factors may lead to incontinence (17,24).

Dysfunction of the sphincters is believed to be a major aetiological factor in those who suffer from faecal incontinence. In health, the internal anal sphincter will relax partially in response to a full rectum. This will herald the process of defecation. The transition zone of the anal canal will detect faeces or flatus. This process is also called sampling (See also Chapter 1.2) (25). If the brain identifies that it is an opportune social time to pass gas or have a bowel movement, the puborectalis muscle relaxes, straightening the path from the rectum to the anus. Then defecation may occur. Conversely, the external anal sphincter is very different from the internal sphincter as this muscle induces both voluntary and involuntary continence. If these muscles become severely damaged or weakened, they may not be strong enough to keep the anus closed and prevent stool from leaking. Therefore, damage to any of the sphincter may lead to major symptoms.

Faecal incontinence is considered as a set of symptoms rather than a disease (11). There are many potential causes and many patients have more than one medical reason for FI, which may include:

- Damage to muscles and nerves occurring directly at the time of vaginal childbirth or after anal or rectal surgery;

- Patients with Crohn's disease, ulcerative colitis and irritable bowel syndrome developing faecal incontinence;
- Haemorrhoids, rectal fistula, rectal prolapse;
- Neurologic diseases such as stroke, multiple sclerosis, spinal cord injury, and spina bifida;
- Chronic diarrhoea, parasite infections, medical conditions (diabetes) and laxative abuse.
- Paradoxical diarrhoea / overflow incontinence occurring in chronic constipation. In such cases, stool fills the rectum until it becomes impacted. Liquid stool leaks around the faecal mass simulating incontinence.

Most of the literature and several reviews found that age contributes significantly to the incidence of incontinence (19–21). KS *et al* confirmed this in a systematic review reporting increased FI with age: 5.7% between 15 and 34 years, 15.9% over 90 years (19).

It is not clear if gender alone has a role on the aetiology of FI. Systematic reviews demonstrated that FI equally affect both men (median, 8.1%; range, 2.3%-16.1%) and women (median, 8.9%; range, 2.0%-20.7%) (19,20); however, several studies emphasise the fact that women have more risks than men. Obstetric trauma is commonly described as primary risk factor (26,27). A recent prospective series looked at 100 males and 100 age-matched females with FI (28). It was found that the incidence of prior anal surgery and abdominal surgery was similar between sexes, but females had a higher incidence of previous pelvic surgery. Incontinence scores were higher in the females. Structural sphincter impairment was very uncommon in males, while impaired rectal sensation and functional disturbances of evacuation were more common in men

than women overall. The authors suggest that the pathophysiological mechanism of FI differ between sexes.

Contrary to gender, obesity seems to have a clearer role in FI (29,30). After bariatric surgery or significant loss of weight FI symptoms may improve significantly. However, in all studies the risk of bias due to other factors, including diet and changes in lifestyle, must be taken into consideration (31).

As anticipated, obstetric trauma has a major role in the incidence of FI (31–34). Figures reported in several studies suggest that men and nulliparous women should be differentiated from parous women when the prevalence of FI is examined (17). Women who have delivered vaginally often have a completely different cause for FI. A recent meta-analysis (35) showed that between 77% and 83% of parous women had FI due to sphincter damage demonstrated on clinical and diagnostic assessment. This may also depend on parity. Lawrence *et al* demonstrated that increasing parity is an isolated risk factor to increase the risk of FI (36).

Diarrhoea is an important associated factor that should be always taken into consideration. In a case series published in the Lancet, 51% of the subjects with chronic diarrhoea were also incontinent (37). Non-infectious diarrhoea and other relevant pathologies such as inflammatory bowel disease (IBD) must also be taken into consideration as they will contribute to the onset of symptoms (32).

Risks of FI patients who undergo anal surgery is relatively high (17,38). Sphincterotomy, fistulectomy, fistulotomy, low anterior resection and haemorrhoidectomy are all examples of

anal surgery that may lead to FI. Lateral internal sphincterectomy may cause FI in up to 8% (39). Following a fistulotomy, the risk is even higher (18–52%) (40,41). Haemorrhoidectomy is a risk factor despite the fact that the sphincters are not intentionally divided (42), which in part may be attributed to haemorrhoids acting as anal cushions and thus playing a pivotal role in continence (43).

Several conditions may cause FI. Example of these include diabetes, multiple sclerosis, stroke, Parkinson's disease, myotonic dystrophy, amyloidosis, spinal cord injury, Hirschprung's disease, HIV, IBD, radiation, gastro-intestinal infection (11). It is also important to remember that constipation sometimes may lead to FI (44). Most recent studies have found these symptoms coexist in the majority of FI patients, in keeping with reported figures describing coexistence of FI and urinary incontinence (44,45).

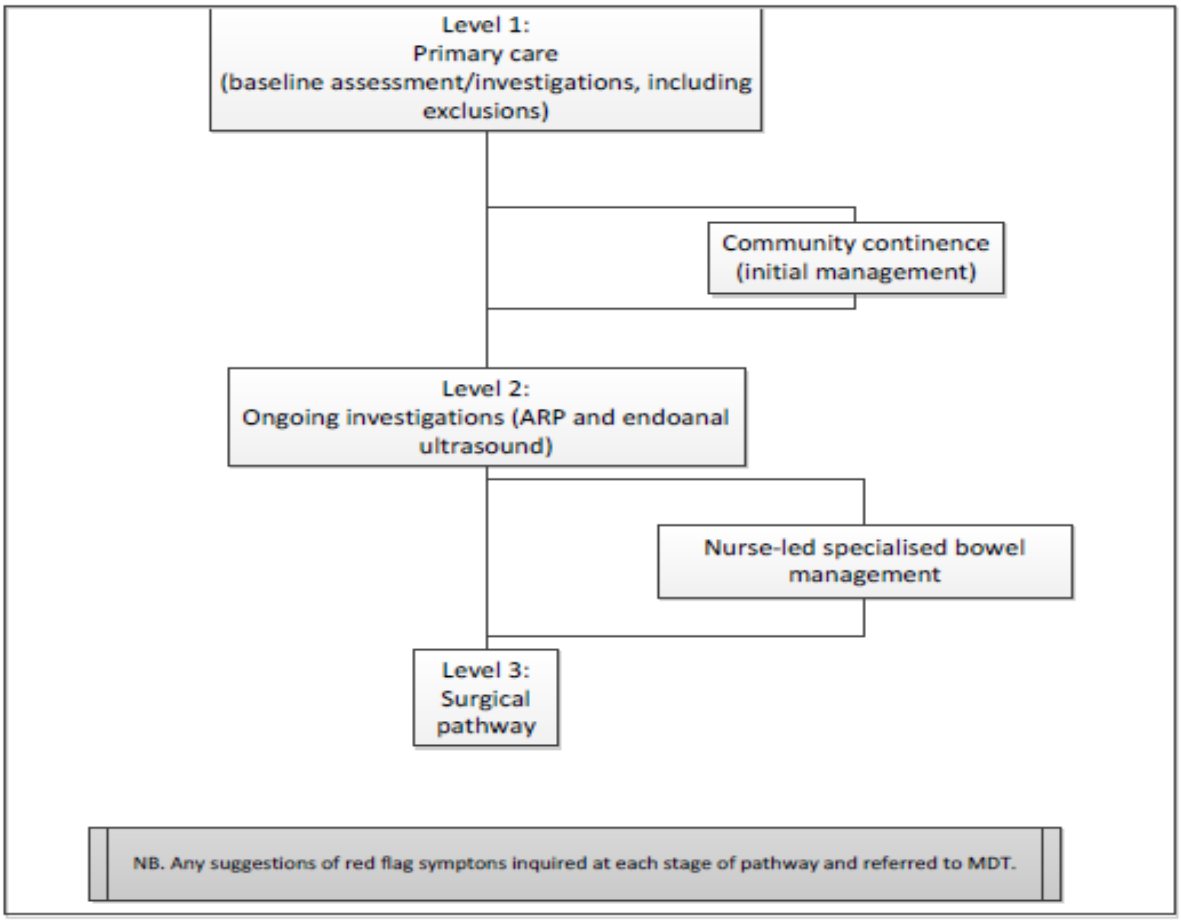
Idiopathic incontinence is of interest. It is most often characterised by low anal squeeze pressures and decreased anal sensation on AnoRectal Physiology tests (ARP). Sometimes this is also associated with low resting pressures and internal anal sphincter atrophy. The aetiology of this is unknown but most likely results from chronic straining during defecation; perineal descent seems to play a role. This subtype of FI results often has a wide variety of clinical presentations and may be a consequence of a combination of factors (46,47).

1.5 Initial assessment

The Royal College of Surgeons of England and the National Institute for Health and Care Excellence provide evidence-based guidelines for the diagnosis and management of FI (Fig.

1.9). These have been recently reviewed and updated (48). These guidelines are a useful instrument to help individualise treatment for those who suffer from this condition. Initial intervention at primary care level is recommended, to ensure that all patients at high risk of FI are identified. Assessment and management of the patient's bowel function should be addressed. This includes a review of medications, diet and advice on the use of continence products. This should be provided by continence advisors who are often community-based clinical nurse specialists (49). After this process is complete general practitioners should refer those who continue to experience FI to secondary care. Reasons for these referrals are patient requests, refractory symptoms, gross sphincter or pelvic floor pathologies or other relevant comorbidities.

Figure 1. 9: Pathway for FI management following the Royal College of Surgeon and NICE guidelines (48).



1.6 Classification of FI

Many authors suggest different classifications of FI and there is no consensus on methods of classifying the symptoms and causes of FI (24,50,51). One of the simplest and most commonly used ways to classify FI is to establish three grades (11):

- Incontinence 1: inability to retain gas;
- Incontinence 2: inability to retain liquid stools;
- Incontinence 3: inability to retain solid stools;

FI can also be classified as follows (52):

- Urge incontinence: when someone feels the sensation of a full rectum and feels the urge to go to the toilet, but they may have to rush to the toilet to make it on time;
- Passive incontinence is when there's no urge instruction to go to the toilet. The person is unaware that the rectum is full and ready to empty. Because patients never feel any sensations in their anal canal, they can't consciously control their bowel movements and stool, in any consistency, is passed without their knowledge;
- Mixed incontinence: when both the above conditions coexist;

However, this method does not address the causes of the incontinence and for the majority of cases incontinence is a very complex scenario with an overlap of these symptoms. Very often patients present with mixed incontinence and also they more often present with symptoms of obstructed defecation (44). Therefore, the aetiology of FI can also be used as a classification system (Table 1.1).

Table 1. 1: Aetiological classification of FI (15,53).

Type	Conditions
Congenital	*Spina bifida, myelomeningocele*
Traumatic	*Vaginal deliveries, pudendal nerve injuries, spinal cord trauma, sexual abuse or any other direct trauma, surgical procedures*
Bowel disturbances	*Diarrhoea, constipation*
Medical conditions	*Diabetes Mellitus, stroke, degenerative disorders of the nervous system, multiple sclerosis, brain tumours, gastrointestinal cancer*
Idiopathic	*? Chronic straining on defecation ? perineal descendent*
Anatomical disturbances of the pelvic floor	*Fistula, descending perineum syndrome, rectal prolapse*
Anorectal inflammation	*Radiotherapy, Inflammatory Bowel Diseases, anorectal infections*

1.7 Special assessment and diagnosis

At secondary care level, patients are usually assessed with ARP testing including anorectal manometry and Endo Anal Ultrasound Scan (EAUSS) to assess sphincter function and anatomy respectively (54). The majority of these patients will be seen by specialist nurses with significant experience in the assessment of FI (55). Nurses specialised in bowel management will be able to provide a proper assessment and a wide range of treatments including pelvic floor muscle training, biofeedback, bowel retraining, rectal irrigation, electrical stimulation, anal plugs/inserts, skincare, and psychological support (8,53,55,56). Patients who fail these treatments should have a consultation with a colorectal surgeon who has experience in this field, to determine whether the patient needs surgical intervention (Fig. 1.7). Therefore, only a minority will see a physician to discuss surgical treatments. Patients with difficult conditions such as rectal prolapse or a reparable sphincter defect should also be seen by a colorectal surgeon (47).

Specialist assessment of FI starts with a detailed history (54). This helps to understand the cause of the symptoms. During this consultation, the frequency and severity of incontinence episodes may be estimated using a two or three week stool diary filled out by the patient (47). Bowel diaries are an essential instrument to assess baseline symptoms and also allow symptoms to be re-evaluated during and after treatment. Another validated way to measure the severity of the symptoms is to use a complementary validated incontinence score. The St Mark's Incontinence score (57) and the Cleveland Clinic Score (58) are a commonly used ways to quantify FI. They are both validated tools and are widely used in clinical practice. The Bristol Stool Chart (11,59), which evaluates the stool consistency, and the Faecal Incontinence Quality

of Life score (FI-QoL), which measures any FI related impairment in quality of life, may also be used (60).

An examination should be always performed in the first instance. It is also essential to exclude non-functional causes such as colorectal malignancy and IBD. The examination may ascertain the presence of anal sensory or motor deficit and the anatomy of the perineum and anal sphincter complex. It should include a digital rectal examination (DRE) and be completed by the use of anoscopy or rigid sigmoidoscopy (61).

ARP tests include anorectal manometry, sensory test, endoanal ultrasonography (EAUSS) and defaecography. These are essential tools to measures the anorectal function and anatomy. Additional tests may be also performed depending on the results and specific conditions: this may include plain x-rays, CT or MRI scans.

Despite the wide array of diagnostic tools available, it is important to bear in mind that no one single test can fully characterise the cause of FI and any other anorectal functional disorders. Some argue that a full clinical examination is not only essential but also a sufficiently adequate method for diagnosis and treatment of these conditions (61,62). On the other hand, there are data to suggest that these objective tests can influence and improve clinical decision making. A general consensus has only recently been achieved and it is now generally accepted that the clinical utility of tests improves when the anorectal function is assessed in a structured and systematic manner (63).

1.7.1 Anorectal manometry

Anorectal manometry measures the pressures within the anal canal and distal rectum. It is one of the most accepted and widely used investigations to measure the function of the anorectum and it is also a valid tool for the diagnosis and management of patients suffering from FI (64). In strict terms manometry is limited to recording the pressure values of the anal canal, however, this test is also performed with concomitant assessments of anorectal sensitivity and anorectal function. The first is normally assessed by the use of electro-sensitivity thresholds, the second is assessed by anorectal balloon expulsion tests.

Pressure assessment of the anal canal includes measurements of resting sphincter pressure, squeeze sphincter pressure, and the functional length of the anal canal. Maximum resting anal canal tone is the pressure that is steady and constant at rest without significant peaks and predominantly reflects internal anal sphincter function (IAS). Maximal resting anal pressure is defined as the difference between intra-rectal pressure and the highest recorded anal sphincter pressure at rest, with this generally recorded 1-2 cm from the anal verge. Maximum squeeze pressure is defined as the difference between the intra-rectal pressure and the highest pressure that is recorded at any level within the anal canal during the squeeze manoeuvre (65). As such, voluntary anal squeeze pressure reflects external anal sphincter (EAS) function. Functional anal canal length is defined as the length of the anal canal over which resting pressure exceeds that of the rectum by greater than 5 mmHg or, alternatively, as the length of the anal canal over which pressures are greater than half of the maximal pressure at rest (66). The length of the anal canal where the pressure is 50% or more of the maximum resting anal tone is defined as the high-pressure zone.

The recto-anal reflex can be recorded during ARP. This is a compensatory guarding mechanism which allows a positive anorectal pressure gradient to be maintained during transient increases in intra-abdominal pressure (such as coughing), which is essential for preserving continence (65). Often, in those with FI, anal sphincter pressure is not increased above the intra-abdominal pressure during coughing, which may contribute to episodes of FI. The recto-anal reflex is also known as involuntary squeeze pressure and can be easily recorded by asking the patient to cough during ARP (67).

The recto-anal inhibitory reflex (RAIR) is another mechanism that can be assessed during ARP (67,68). This is when the rectum is dilated suddenly, the rectal wall contracts, the external anal sphincter muscle contracts temporarily, and the anal resting period pressure is elevated (anorectal contraction reflex). Immediately after this occurs, there is a decrease in the resting pressure, and the internal anal sphincter muscles relax temporarily. This sequence of events is the anorectal inhibitory reflex. It is important to record these reflex activities especially in patients with a suspicion of colonic aganglionosis (Hirschprung's disease) where the anorectal inhibitory reflex is absent.

For the reasons outlined above anorectal manometry is an essential test for investigating patients who suffer from FI. It allows the measurement of anal resting and squeeze pressures, which are considered as surrogate markers of internal and external sphincter function (69). Despite the use of these investigations, it is recognised that a small group of patients may have symptoms of FI and yet have normal anorectal function parameters. This may be due to the multifactorial pathophysiology of FI, but may also reflect the suboptimal nature of current manometric technology (63,69). Over the last 50 years, manometry has evolved and there are

numerous technologies now available. The current water perfused catheters contain several closely spaced circumferential sensor elements along the longitudinal axis. The pressure-sensing element varies between commercial systems. Commercially available catheters come in a variety of configurations with four, six, twelve or even thirty-six circumferential sensors, depending on the manufacturer and preferred technology chosen. Since 2007 software has been available that allows manometry catheter readings to be displayed in high resolution or 3D high resolution images (70,71).

Solid-state catheters are also available and include either eight or twelve circumferential sensors, with different technologies and software depending on the commercial supplier. These are more reliable than water perfused catheters but are often fragile, structurally very susceptible to temperatures out with the standard ambient room or physiological range, and also commonly more expensive (63).

ARP tests may also measure anorectal sensitivity. An intact anoderm, nerve endings in mucosa and submucosa, afferent fibres in the pudendal nerve, and the central nervous system with spinal cord and brain, all play a role in anal sensitivity. Both symptomatic and asymptomatic patients who have anal abnormalities can have disturbed anal sensitivity (72). Therefore, these tests should be included in a full evaluation of anorectal function (63).

1.7.2 EAUSS

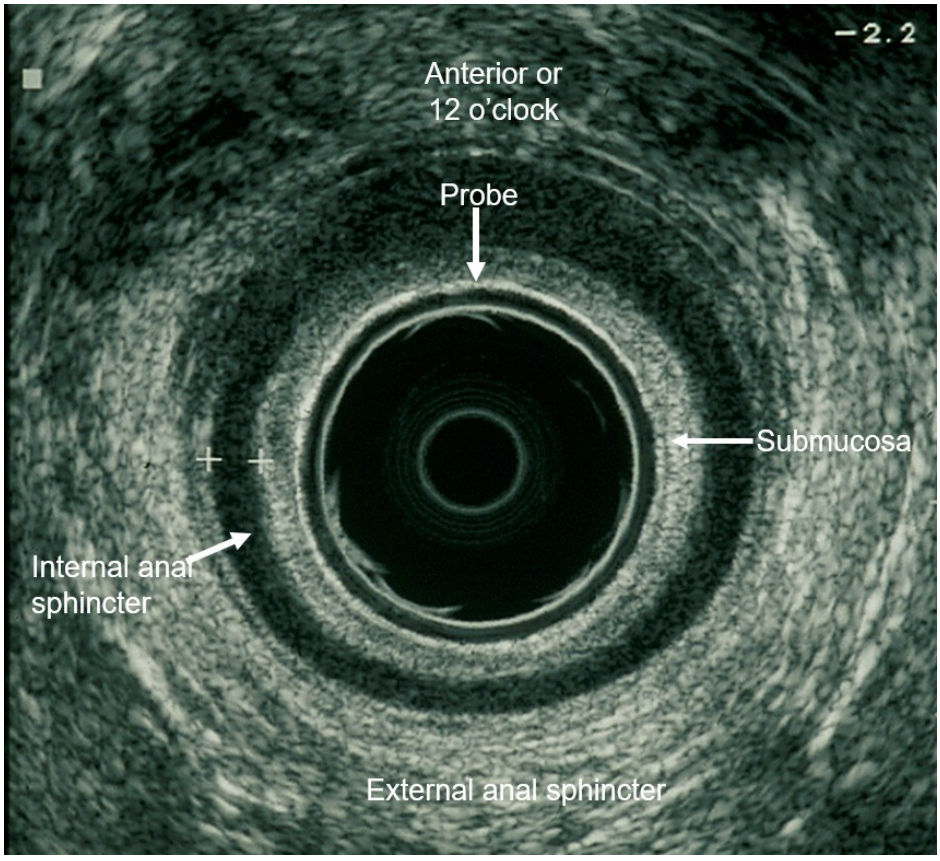
An endoanal ultrasound scan (EAUSS) is a complimentary test to ARP as it can evaluate anatomy and anal sphincter integrity (73,74). It was initially invented in the 1980's by Professor Clive Bartram, Consultant radiologist at St Mark's Hospital (73). Since then many

types of EAUSS have been developed. Currently there are two models available with different frequency options (7.5 MHz and 12 MHz). Both are very accurate and provide excellent quality in defining anorectal anatomy (75). Also, the current technologies provide both 2D and 3D assessment of sphincter anatomy. These images come from the same probes, however the processing and the image acquisition is different. It should be noted that the 3D technology can provide even finer assessment. Both technologies have the advantage of avoiding exposure to radiation but they rely on the operator for accuracy (73,75).

EAUSS is now considered an essential adjunct to ARP as it can evaluate defects in anal sphincters, which may for example be a prior injury that occurred during traumatic vaginal delivery (76). The internal and external sphincters can be evaluated separately. Various angles are measured with the patient at rest and during maximal voluntary contraction of the puborectalis.

During assessment, the operator can delineate the anatomy of five or possibly six hypoechoic and hyperechoic layers. The hypoechoic layer that represents the internal sphincter muscle has a thickness that can vary from 1.5 to 4 mm and increases with the age. The average thickness of the external sphincter muscle varies between 8.6 ± 1.1 mm in males and 7.7 ± 1.1 mm in female (Fig. 1.10). The longitudinal muscle is 2.5 ± 0.6 mm in males and 2.9 ± 0.6 mm in females. This muscle appears on EAUSS moderately echogenic (75).

Figure 1. 10: Normal anatomy of the anorectal sphincter complex seen in a 2D EAUSS technology. Here is shown the normal anatomy with the traditionally hyperechoic internal anal sphincter (IAS), the hyperechoic external anal sphincter (EAS) and the typically hyperechoic longitudinal muscle (a continuation of the longitudinal muscle layer of the rectum). Image from St Mark's Hospital Academic Institute archives: Dr Arun Gupta (Consultant Radiologist, St Mark's Hospital), "Anorectal Physiology" Jan. 2019, PowerPoint presentation.



1.7.3 Other tests

Defecography can also be used to investigate anorectal abnormalities and can be a useful instrument to investigate refractory faecal incontinence, although this is not a first choice test for this condition (77). This technique uses a luminal contrast, usually liquid barium suspension, which is placed within the rectum. This is often mixed with a thickening agent, usually potato starch or porridge oats, to form a consistency similar to soft stools. A series of radiographs or fluoroscopy are obtained whilst the patient is sitting on a commode simulating a defecation attempt. X-ray defecography can measure the anorectal angle, the position of the pelvic floor at rest or during a Valsalva manoeuvre to diagnose perineal descent. It can also reveal the presence of a rectocele and rectal intussusception. A Valsalva manoeuvre can also evaluate the ability of the patient to expel rectal contents.

MRI technology has been recently added to the armamentarium of defecographic techniques (78) but is expensive and thus is not widely available. Also, the patient is asked to lay flat on the MRI gantry during expulsion rather than sitting on a commode, providing a less natural position to simulate defecation. For these reasons, this test has not been widely adopted.

Electromyography (EMG) was once used for localization of sphincter defects and can characterize muscle function by recording the electrical activity (79). Traditional concentric EMG uses a probe that is inserted manually either into the puborectalis or external anal sphincter. Manoeuvres, such as rectal balloon distension, saline infusion or perianal pinprick, are then performed to elicit reflex contraction of the sphincter. It is not in use anymore as it is considered too invasive; however, over the last few years companies have developed less

invasive technologies to simulate traditional EMG that are now used for both diagnosis and biofeedback treatment (80).

1.8 Management of Faecal Incontinence

1.8.1 Conservative treatments

As per the recommendations provided by national and international guidelines, the treatment of FI is mainly conservative and is often guided by the severity of the reported symptoms, the aetiology and the function of the pelvic floor. Continence advisors (CA) are essential in the community and their first-line therapy can treat and improve quality of life for the majority of patients suffering from FI. In the UK this is a well-established community service, mainly represented by the Association of Continence Advisors (ACA) (49). First-line therapy should include a full assessment of patient symptoms, history and an examination including a digital rectal exam (DRE). Treatment should focus on dietary modification, lifestyle changes, prescription of specific medications including suppositories and anti-diarrhoeal agents. Ideally, pelvic floor muscle exercises and physiotherapy should also be part of their routine care.

Patients referred to secondary care will be offered more specialist treatment. A multidisciplinary team should address treatment to provide more holistic care. Specialist dieticians can also provide dietary modifications to improve symptoms. These modifications may aim to increase fibre in daily regime to improve stool consistency. Sometimes stool bulking agents are used with the same aim. When stool consistency is too loose, anti-diarrhoeal agents should be prescribed starting from a low dose that can be increased as needed. Low doses are essential to avoid side effects such as constipation. To improve soiling, phosphate

enemas may be prescribed. When these fail, low, intermediate and high volume irrigations may help to manage incontinence symptoms especially in those cases where faecal impaction is present.

1.8.1.1 Biofeedback

Biofeedback (BFB) is an even more specialised range of treatments and is also known as behavioural therapy. It was introduced for the first time more than 40 years ago (81) and it uses visual, auditory and or verbal feedback techniques (8,55,56). This should only be undertaken by specially trained nurses in centres with an interest in pelvic floor disorders. BFB aims to improve strength, sensory and coordination training to improve symptoms of FI. Patient collaboration is essential to achieve good results. Patients are normally taught to improve their ability to voluntarily contract the external sphincter during rectal filling, by improving the strength of the sphincter (motor skills training), or by the increasing the ability to perceive weak rectal distension (discrimination training), or by combining these two described mechanisms (82). More recent studies demonstrate that BFB may significantly improve symptoms (64 - 89%) (77,83). The mechanism of efficacy is not completely defined but must be taken into consideration that it is painless, without risk, completely non-invasive and it is generally well accepted by patients. BFB should also incorporate pelvic floor muscle exercises and physiotherapy, when required, to achieve better results (55).

1.8.1.2 Anal plugs

Anal plugs can be part of first line treatment. They are non-invasive and safe (84–87). They are normally disposable and different forms of these anal inserts are available. All aim to reduce passive incontinence by blocking the passage of stool from the anal canal. They are more

efficient when used to prevent soiling of liquid stools and very helpful in patients with decreased anal canal sensation. The most used and known products are:

- The Conveen® anal plug (Coloplast, The Netherlands) which is a single-use, disposable polyethylene plug with a compressed conical apex and a removal cord which, after insertion, settles into the anal canal for simple closure. It consists of compressed foam in a conus shape with a removal cord at one side. It is normally introduced in the anus with the cord hanging out. After introduction, the plug will extend within 30 seconds to its maximum size, thus closing off the anus (Fig. 1.11).

- The Renew™ anal insert (Renew Medical Inc., Menlo Park, California, USA) which is a single-use anal device that is to be used continuously with the aim of managing the symptoms of passive and mixed FI. The device can be inserted by the patient with a fingertip applicator. It is made from soft, supple silicone that adapts to the patient's anal contours. It is available in two sizes, regular and large. They are considered safe to wear day and night, and are simple to remove (Fig. 1.12).

Although both device are a fascinating alternative conservative treatments for FI, reviewing the literature data relating to the use of anal plugs / inserts for the management of FI are limited by small numbers, short-term outcome assessment and a lack of randomised and comparative data (88).

Figure 1. 11: The Peristeen® ‘tulip’ Anal Plug. From https://www.coloplast.co.uk/peristeen-anal-plug-en-gb.aspx, access on 21st September 2020.

Figure 1. 12: The Renew Anal Insert. From https://renew-medical.uk/products/renew-insert/, access on 21st September 2020.

1.8.1.3 Percutaneous Tibial Nerve Stimulation (PTNS)

Percutaneous Tibial Nerve Stimulation (PTNS) is a non-invasive, safe and inexpensive treatment for FI (89,90). PTNS is usually delivered unilaterally, at the most superficial position of the tibial nerve, which lies above and behind the medial malleolus (Fig. 1.13). Patients need to attend one or two sessions per week for six or 12 consecutive weeks (89). Three prospective studies of PTNS from the same institution have used either once a week or twice a week treatment strategies with no apparent differences in efficacy (89–92). The superiority of one approach over the other remains to be demonstrated; however, Thomas *et al* in a prospective randomized control trial demonstrated that daily treatment may be more effective than a twice a week in hospital use (93). Data from published case series suggest PTNS has beneficial outcomes in up to 80% of patients. However, a more recent multicentre double-blind randomized control trial demonstrated that 12 week PTNS treatment did not confer significant benefit over sham electrical stimulation in the treatment of FI, therefore its efficacy is still uncertain (94). Currently it is unknown whether PTNS treatment is associated with only a placebo effect or whether improving neuromodulation parameters, patient selection, and the frequency of maintenance sessions can deliver genuine improvements in FI symptoms (95–97).

Figure 1. 13: PTNS treatment has been proved to be a safe, non-invasive treatment for FI. In this figure the device with the needle inserted unilaterally at the most superficial position of the tibial nerve. Courtesy by Laborie Medical Technologies.

1.8.2 Invasive treatments

When patients fail all conservative treatment options they may be considered for surgical treatments. Once again a multidisciplinary approach is essential and all of these patients should be discussed at a multi-disciplinary pelvic floor meeting (MDT) to exhaust all possible conservative treatment options before surgery. Findings demonstrate that joint pelvic floor MDT meetings are beneficial and may change the management of complex patients (98).

1.8.2.1 Sacral Neuromodulation (SNM)

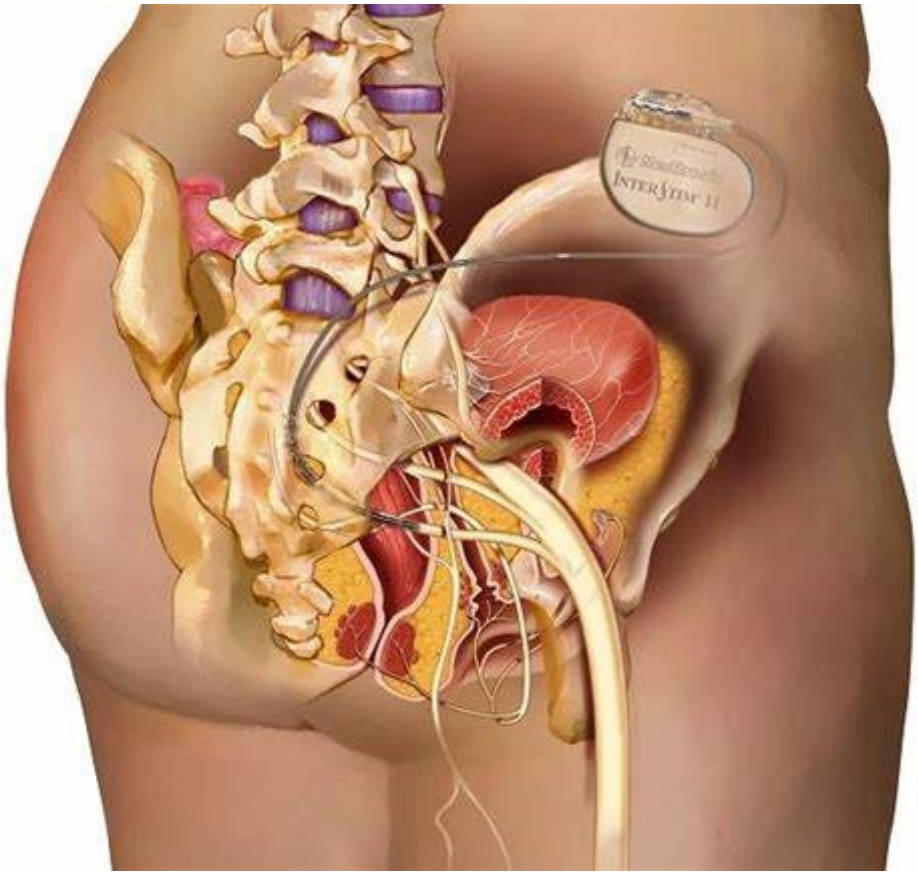
Sacral Neuromodulation (SNM) is an accepted treatment for faecal incontinence as well as an established treatment for urinary incontinence (99–101). The mechanism of action of SNM is complex and multifactorial and underlying mechanism of action remain unclear. Neuromodulation involves chronic stimulation of the sacral nerve roots, which supply the anorectal sphincter complex and the pelvic floor (Fig. 1.14) (102). It has been proved that most of the increased anal pressure with SNM is attributable to contraction of the striated musculature, however an effect on the smooth muscle of the internal anal sphincter cannot be excluded. There is also the possibility that the autonomic nervous system might be affected reflexively by somatic neurostimulation, although this has never been proved yet. Traditionally, the sphincter acting as a barrier had primacy as main mechanism on the pathophysiology and surgical management of FI. Sphincter disruption is still relevant to the development of FI in many patients, however this is only one factor in a more complex defaecatory dysfunction that involves alteration in unconscious anorectal and pelvic reflexes and conscious modulation by the central nervous system. In fact, although SNM was developed for FI with the view that it would augment defective sphincteric function, it is now well appreciated that patients with FI resulting from pathophysiology other than primary

sphincter dysfunction also benefit from treatment. The importance of sensory dysfunction on both urinary and bowel control is being increasingly appreciated and there is current evidence that the mechanism of action of SNM results primarily from modulation of afferent nerve activity. More recent trials to clarify this points have been designed and are currently in progress (103).

The SNM technique is well standardised (102). Patients are first evaluated for suitability of the procedure. This phase of the procedure can currently be performed in two different ways. Historically the most common strategy was to insert a temporary external wire (PNE, Peripheral Nerve Evaluation), which is left in place for two to three weeks. Alternatively, a more advanced lead (used for chronic stimulation) may be used for this test stage. This can be left in place if a successful test stage is experienced. Those who respond favourably, with at least a 50% improvement in symptoms, may be offered a permanent implant. Regardless of the PNE strategy the aim is to place the lead into the third sacral foramen. The permanent lead incorporates four equally spaced electrodes on a flexible curved lead inserted percutaneously under image guidance and anchored in place by several barbs that contact with soft tissue and bone in the corresponding sacral foramen. This is then connected to an implantable pulse generator (IPG), which is placed in a subcutaneous gluteal pocket. The stimulation can be activated and adjusted by an external remote controller. The four electrodes can be activated singly or in combination to produce an electrical field that interacts with the target nerve. A closer electrode to the target nerve provides a higher likelihood for optimal effect with longer battery longevity (102). It has been estimated that approximately 25% of patients fail the test phase (104,105). Despite the elevated cost of the implant, the minimally invasive nature of SNM, its reversibility and the fact that the potential clinical effect can be assessed before

chronic therapy has led to its general acceptance (106,107). Based on patient selection by test stimulation, clinical improvement with permanent SNM is achieved in about 80% of patients with FI in the medium to long term (108,109).

Figure 1. 14: Sacral Neuromodulation is an established treatment for patients who suffer from FI. Neuromodulation involves chronic stimulation of the sacral nerve roots. Courtesy of Medtronic UK.



1.8.2.2 *Bulking agents and injectables*

This technique relies on the bulking effect of the injected material into the anal sphincter with subsequent fibrosis and collagen deposition (110,111). The optimal site to place implants is also thought to depend on the material used. It has been suggested that these therapies may be most effective for "gutter" type sphincter deformities or passive seepage. A systematic review raised concerns about their overall effectiveness and safety (112). In some cases application may need to be repeated if efficacy diminishes (113,114). Newer bulking devices include the Gatekeeper (115,116) and, its successor, the Sphinkeeper (117). These techniques work by the injection of multiple self-expanding devices of polyacrylonitrile (polyvinyl cyanide and Creslan 61), which once placed enlarge their diameter multiple times. Small studies with short term follow up follow up suggest promise, but this yet to be confirmed by larger trials (117,118).

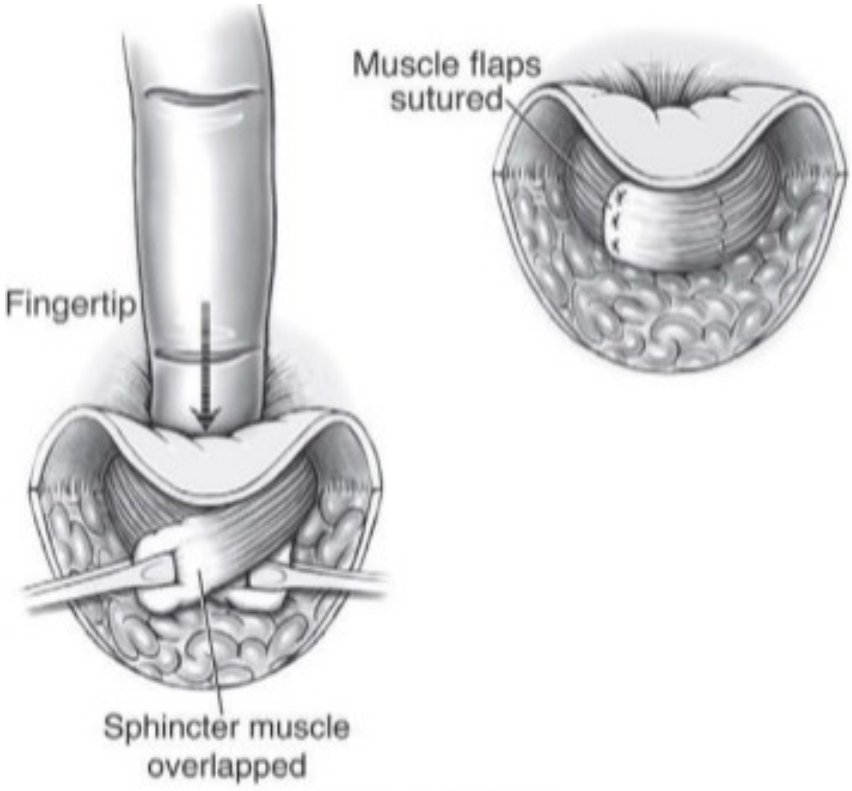
1.8.2.3 *Sphincter repair and pelvic floor reconstructions*

Sphincter repair and more complex pelvic floor reconstructions are valid surgical options (48,119) when a full length sphincter defect has been demonstrated and when more non-invasive procedures fail. Overlapping sphincter repair (Fig. 1.15) was initially described by Parks and Mc Partlin (120) in 1971 and by Fang *et al* (121) in 1984. Since then, it has been used to repair full-length external anal sphincter defects with the aim of improving urgency. Injuries to the anal sphincters may be sustained during childbirth or following surgery, and anterior sphincter defects may not be identified immediately and may be repaired only many years after the occult injury. This operation is carried out through an anterior incision. The divided ends of the external anal sphincter are identified and either approximated or more commonly overlapped and suture repaired. In general, most published series report subjective

outcome measures with the majority of patients said to consider their function to be "good", with a deterioration in symptoms over longer follow-up (112). Despite this deterioration in effectiveness, patient satisfaction remains good and the procedure can be repeated.

More complex procedures have been proposed and developed with the aim of replacing the sphincter when a repair is not possible or has failed. These include the dynamic graciloplasty (DGP), gluteoplasty, or artificial anal sphincter. DGP aims to recreate a sphincter using the gracilis muscle from the adductor compartment of the thigh and encircling it around the anus. A nerve stimulator is then inserted to make the muscle contract tonically (122,123). The gluteoplasty transposes one or both gluteus muscles from the buttock and uses them to encircle the anal canal (124). The artificial anal sphincters are either metallic or silicone made cuffs that encircle the anus (125,126). DGP and gluteoplasty have been demonstrated to be quite effective between 50 – 80 % of the cases in the long term (127). However, significant morbidity has been reported, such as, pain infection and donor site problems (122,123). Evacuatory problems and constipation are reported too (127–130). Because of these issues, these procedures are rarely performed today. Artificial anal sphincters were initially promising but further reviews demonstrated that high morbidity rate occur infection and erosion. Device removal rates are high, ranging from 17% (under 2 years follow-up), 1 to 44% (4 years follow-up). A device removal rate of 30% (1-year follow-up), from a large multicentre study (112 patients) was reported (131–133). This technique has now been abandoned in most countries.

Figure 1. 15: overlapping sphincter repair technique. From www.alpfmedical.info, access on 5th June 2020.



1.8.2.4 *Stoma*

A small group of patients who fail all non-invasive approaches and with end stage FI may be considered for a stoma (Fig. 1.16 and 1.17). This is usually a colostomy (134) and may provide a substantial improvement in quality of life. Norton *et al* in a patients' view survey reported that 83% of patients interviewed felt that the stoma restricted their life 'a little' or 'not at all'. Also, 84% of them stated that they would 'probably' or 'definitely' choose to have the stoma again. Although stoma is an invasive treatment, Norton *et al* study results suggested that the majority of the previously incontinent interviewed patients have an overall positive feeling about stoma (135).

Figure 1. 16: Formation of a loop colostomy. With courtesy of Marc I. Brand and Nadav Dujovny (134).

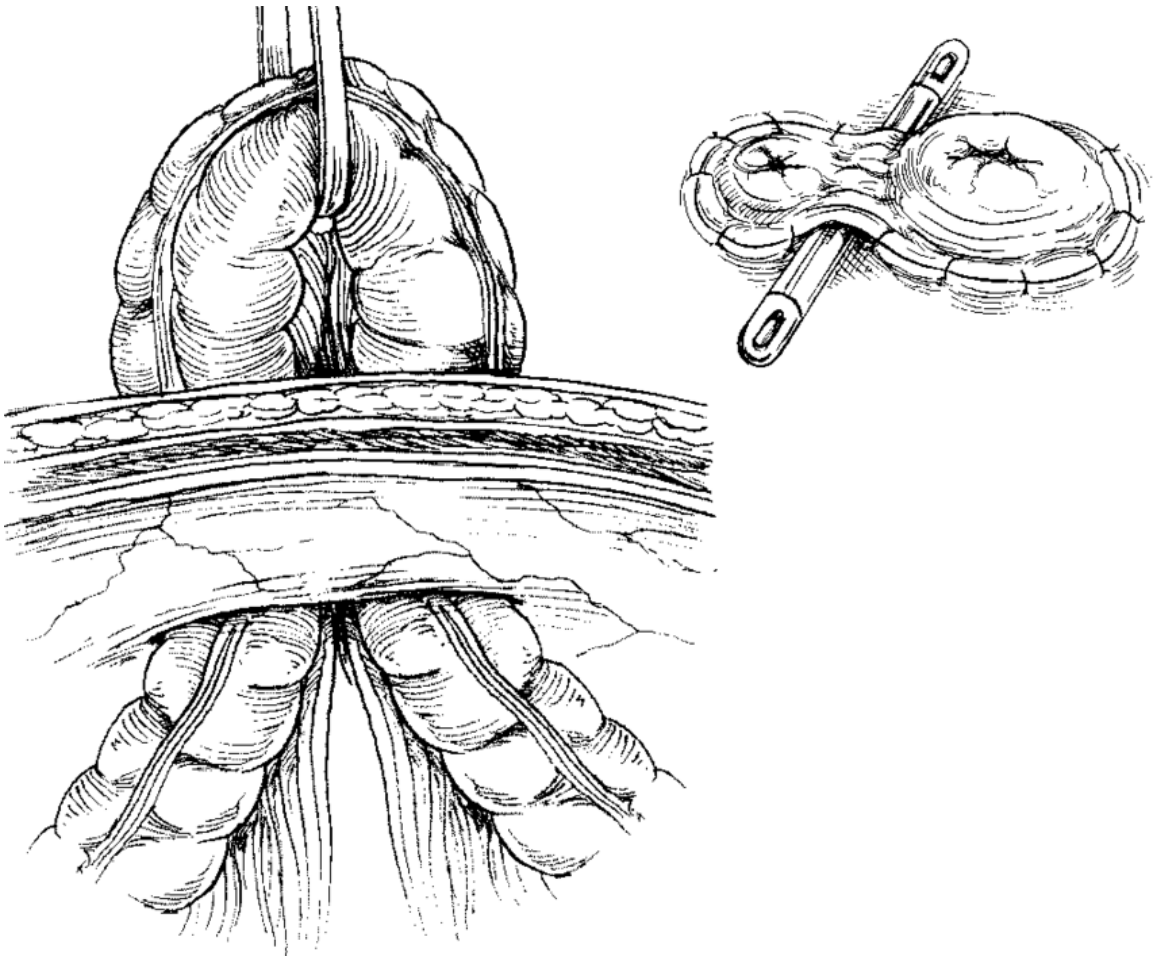
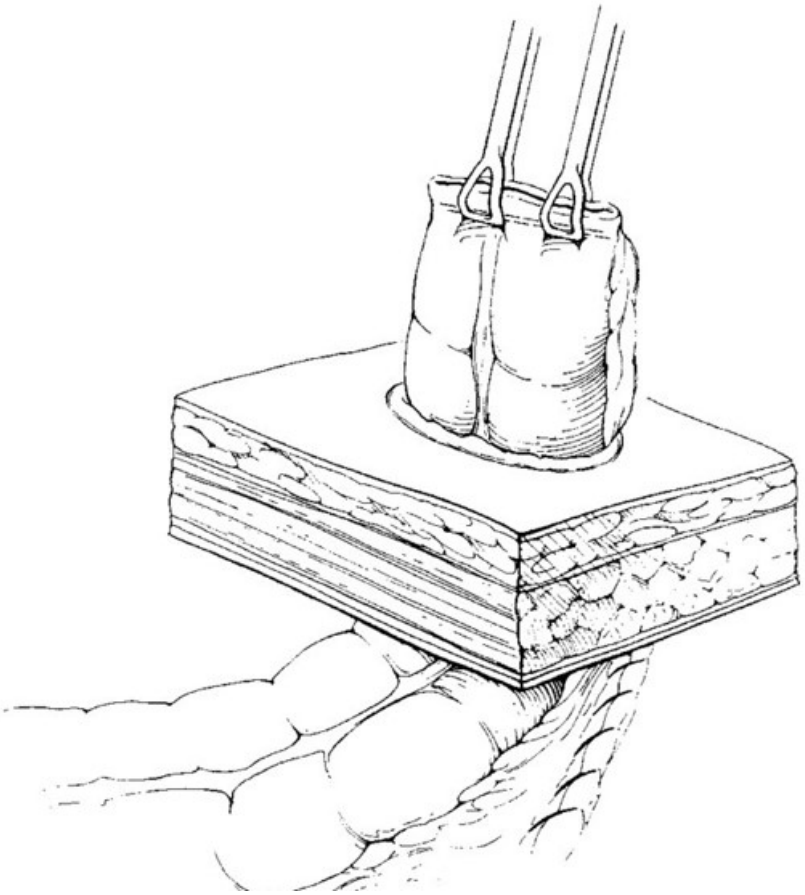


Figure 1. 17: Formation of an end colostomy. With courtesy of Marc I. Brand and Nadav Dujovny (134).



1.9 Hypothesis and aims of this thesis

Hypothesis: Can diagnosis and treatment of faecal incontinence be improved?

Aims: This thesis investigates the current practice of continence advisors in the community in the United Kingdom. It also assesses and evaluates a new generation diagnostic manometric device (THD® Anopress). This will involve deriving normative values for this diagnostic tool, evaluating this device in the clinical practice and finally comparing this new tool to the more widely used technique of water perfused anorectal manometry. Further aims are to investigate a new first line treatment for FI (Renew™ Anal Insert) and finally to compare this to another well-established non-invasive treatment, Percutaneous Tibial Nerve Stimulation (PTNS). It is also aim of this thesis to report the long-term effectiveness of Sacral Neuromodulation (SNM) and to describe the first experience with a new bulking agents, the Sphinkeeper™.

2 Current available support in the community

2.1 Evaluation of a Continence Advisor Survey in the UK

2.1.1 Introduction

Faecal incontinence (FI) is a common symptom. It is most common in the elderly, with a prevalence of 1-18% (7,15,21,136). Concomitant urinary incontinence is common and may occur in 6.5% of women approximately 15-23 years after their first vaginal delivery (36,137). Patients may not receive adequate treatment for faecal incontinence for many reasons. These include social stigmatisation, embarrassment, or failure to recognise this as a treatable condition (137).

Faecal incontinence is a condition frequently encountered by coloproctologists. There are a variety of invasive treatments available. These include sphincter repair, sacral nerve stimulation and artificial bowel sphincter implantation (53,138). However, the benign nature of this problem and the varying degrees of severity, mean that conservative management is usually pursued first (8). It is likely that ongoing conservative treatment and follow up in the community is also required following any surgical interventions to achieve a successful outcome.

Continence advisors (CA) provide primary care in the community across the UK for patients seeking help for their incontinence symptoms (49). Most are clinical nurse specialists who work at General Practice surgeries or health centres and teach pelvic floor exercises and introduce patients to continence pads and products. The service is well established for urinary

incontinence, and in recent years has provided care for faecal incontinence (139,140). Many of those who have not been referred to hospital are managed by these practitioners. However, there are no available data to assess the structure and competence of this practice.

Recent National Health Service (NHS) Commissioning Guidelines place great emphasis on continence advisors delivering first line therapy in the community setting (48,141). They are expected to have systems in place to ensure that patients who are at high risk of faecal incontinence are identified. They should be able to carry out a baseline assessment, such as the history of bowel symptoms and establishing it the patient has any 'red flag' signs of colorectal cancer. The patient's bowel habit pattern should be established and there should be a medication review. A visual anal and digital rectal examination should be undertaken to exclude faecal impaction with overflow, and to assess anal tone and squeeze pressures.

The guidelines further recommend that initial bowel management should include instruction on dietary modification, supervision of appropriate medications and advice on use of continence products. All patients should be offered reassurance and lifestyle advice, access to help with relevant physical, emotional, psychological and social issues, advice about relevant support groups and advice regarding self-management of symptoms (141).

The purpose of this study was to investigate the current practice of community continence advisors in the United Kingdom. This assessment included the extent of treatment options offered by continence advisors and if they felt there was a need for further support for this community service.

2.1.2 Method

An online survey was constructed using Survey Monkey® (Online survey services, Palo Alto, CA, United States). The questions used were composed by my supervisors, both of whom have extensive experience in the management of faecal incontinence. Firstly, relevant topics were discussed, and three topics were chosen to be the focus of the questionnaire. These were assessment, treatment and education. In addition, baseline demographic data of the continence advisors was included. The questions were drafted by two of the authors and approved at weekly pelvic floor departmental meetings where biofeedback nurses, pelvic floor physiotherapists, colorectal surgeons and a gastroenterologist gave feedback on design of the questions and of this study. A total of five meetings were held. In the final version, the survey consisted of 27 health related questions which were separated into seven different sections. The survey was designed to obtain a snap-shot of current practice of continence advisors and was not validated as a questionnaire.

The respondents were not obliged to answer each question; therefore, the denominators of the numbers expressed as a percentage in the results section are the number of the responders for each question. Continence advisors in the UK were identified from the authors' departmental database and from the UK Association of Continence Advisors. All continence advisors were invited to complete the online survey via email, mail and phone calls. A £50 voucher was given to a randomly chosen respondent, in an effort to increase the response rate. Email invitations and reminders were sent via Survey Monkey® eight times over a three-month period. At the end of this three-month period, the survey was closed. Responses were collected and analysed, initially using the Survey Monkey® software and then again with Excel (Microsoft Corporation, USA). The survey questions are outlined in Table 2.1.

2.1.3 Results

The questionnaire was split into seven different sections (demographics, assessment, treatment, factors influencing choice of treatment, educational support, treatment failure and adequacy of training). There was also an additional question asking for general feedback. Between October 2015 and December 2015 (three months), 226 responses out of 448 UK Continence Advisors (50.4%) were collected. For each question there was a different number of responders with a median of 213 (range 164 – 226) responders.

2.1.3.1 Demographics

Of the 226 responders, 93.2% were female: 4.9 percent were between 30 and 39 years old, 62.8% were between 40 and 59 years, 25.6% were between 50 and 59 years and 6.7% were over 60 years old. Some 91.1% were previously employed as nurses, while the remainder had been specialist nurses or physiotherapists.

Of the continence advisors, 13.1% had less than 5 years experience as a CA, 28.4% had between 5 and 10 years experience, 46.9% had between 10 and 20 years experience and 11.7% had more than 20 years experience. Thirty-six (16.1%) worked alone, while 177 (79.0%) worked with other Nurses, Physiotherapists, or a General Practitioner, 10 CA (4.5%) answered they worked alone as well as with other Nurses or Physiotherapists, and 1 CA worked with a GP. Fifty-one CA (23.1%) treated urinary incontinence, while 76.9% treated both urinary and faecal incontinence.

Regarding their service, 6 (2.7%) of the CA see an average of less than 5 patients with urinary incontinence per month, 59 (26.8%) see between 5 and 20 patients, 98 (44.6%) between 20 and

50 patients and 57 (25.9%) more than 50 patients with urinary incontinence per month. With regards to faecal incontinence, 66 (33.5%) see less than 5 patients, 107 (54.3%) between 5 and 20 patients, 18 (9.1%) between 20 and 50 patients, with 6 (3.1%) seeing more than 50 patients with faecal incontinence per month.

2.1.3.2 Assessment

A total of 167 (75.6%) of CA perform a digital rectal examination as part of their assessment, and 159 (95.2%) of them felt confident in their ability to do this. One hundred and thirty one (61.2%) assessed patients for the presence of a rectal prolapse, of these 114 (87.0%) felt confident in their ability to do this correctly. EMG (Electromyography) of the anal sphincter was used by 9.1% of CA.

2.1.3.3 Treatment

Loperamide was recommended regularly by 83 (39.0%) of respondents. Just over 3% (n=6) prescribed a range of other medications such as co-phenotrope, colesevelam and cholestyramine. Probiotics were recommended by 64 (30.2%) of CA, charcoal was recommended by 6 (3.1%) and 16 (8.2%) recommended Aloe Vera. Most practitioners were able to give advice on diet, including low fibre diet 156 (77.6%), high fibre diet 185 (85.3%) and FODMAP diet 51 (30.2%). With regard to the use of suppositories, enemas and rectal irrigation, 148 (69.5%) prescribed glycerine suppositories, 127 (61.4%) prescribed phosphate enemas and 147 (68.1%) advised on rectal irrigation. The remaining results of the treatments available are shown in Table 2.1. It should be noted that 221 out of a total of 226 respondents were able to offer treatments for faecal incontinence.

Table 2. 1: Treatments offered by continence advisors; * Squeezy (Propagator Ltd).

	Number of positive responses	**Percentage of respondents**
Dietary advice		
Low fibre diet	156	77.6
High fibre diet	185	85.2
FODMAP diet	51	30.2
Psychological support		
Sexual dysfunction	110	52.9
Body image	102	49
Depression	98	47.6
Anxiety	111	53.1
Treatments		
Pelvic floor/ sphincter exercises	207	93.7
Urge resistance techniques	188	84.3
Tibial nerve stimulation	21	9.9
Pelvic floor exercise app*	69	31
Peristeen coloplast anal plug	159	71.9
Renew anal insert	78	35.3
Incontinence pads	156	70.6

2.1.3.4 Factors influencing treatment choice

Continence Advisors were asked what would guide the choice of commercial products they use. They were asked to rank from 1 (least important) to 5 (most important) about marketing, cost, patient's choice/preference, practice surgery's choice/preference, and sponsorship. Patient's choice/preference scored the highest (weighted average 4.22) as 48.7% of CA stated this was the most important when they choose products. The least important was sponsorship (weighted average 2.23) with 62.4% of CA considering it was the least important. The influence of marketing was the second least important with nearly half of the CA (45.9%) stating it was the least important. Practice surgery's choice/preference was less important with 47.1% of CA ranking this either 1 or 2, whilst 39.1% of CA considered cost to be a more important factor.

Continence advisor practice following identification of treatment failures was then assessed. One hundred and sixteen (54.5%) CA referred 0 to 20% of their patients onto a hospital based specialist, 59 (27.7%) referred between 20 and 40% to a hospital specialist, 16 (7.5%) referred between 40 and 60% to a hospital specialist, 11 (5%) referred between 60 and 80% to a hospital specialist while 11 (5%) referred between 80 and 100% of their patients who failed therapy to a hospital specialist.

2.1.3.5 Educational support

One hundred and ninety-seven (90.0%) of those who responded attended courses organised by industry, 121 (59.6%) attended courses run by hospitals and 117 (57.6%) attended courses run by universities. Eighty-nine (46.1%) had received sponsorship to support their attendances. When asked if they felt supported in their daily practice, 165 of the 223 respondents (74.0%)

felt they were. Twenty-nine (13.0%) answered no, and 29 (13.0%) were unsure. Eighty-nine (42.6%) felt they had not been adequately trained to provide a bowel continence service.

2.1.3.6 General feedback

Open feedback was collected from 53 respondents. The more useful comments relating to the purpose of the study are outlined below. Five said they were willing to attend educational courses to improve their skills, but had difficulty acquiring funding. One suggested that educational courses should be free. Two of the CA highlighted the fact that they are able to perform a vaginal digital examination and that they have the skills to diagnose a rectocele. One thanked the survey organisers because she was unaware the Squeezy smart phone app existed. That particular CA downloaded and used this app in her practice to good effect.

2.1.4 Discussion

This study has used an online survey to assess the current practice of continence advisors in the UK. The study was undertaken because CA have been given a very significant role to play in the community management of faecal incontinence (83,140,142–144) but as yet there are no available data to assess the structure and competence of this practice. The results of this study broadly suggest that CA provide a reasonable but not optimal service for those with faecal incontinence.

The majority of Continence Advisors reported they are able to confidently perform a digital rectal examination and to look for rectal prolapse. This survey demonstrated that loperamide and probiotics were the most commonly utilised medications. However, they were prescribed

by only 39% and 30% of respondents, respectively. In addition, there appeared to be a poor awareness of other alternatives. This may be accounted for by the fact that many CA were unable to prescribe and were dependent upon the patient's General Practitioner to do this. That said, around two thirds of CAs were able to offer suppositories, enemas and rectal irrigation, which are important treatments for FI. The majority of CAs seemed happy to advice on basic dietary manipulation. However, only around 50% of respondents were prepared to address this.

Over 70% of responding CAs were happy to recommend the Peristeen Coloplast anal plug, and 35% were happy to offer the new Renew anal insert. This may reflect the fact that the latter is relatively new. It is interesting to note that the CAs considered patient choice to be the most important in deciding continence products, despite 90% of them attended industry sponsored courses. Many CAs appear to have found the Squeezy app useful, which is currently recommended by the NHS. As the use of smart phone technology increases over time, the relatively low take up of around 30% should improve.

Three quarters of CAs felt they were adequately supported in their practice, however, just over half felt they had received adequate training, mainly run by industry. It was surprising to find that when their treatment fails, only 5% of CAs referred the majority of such patients to hospital specialist. More than half of the CAs referred up to 20% of patients who failed their treatment. The feedback part of the survey suggested that more than half felt the need for more training, and for this to be more accessible.

There are some limitations to this study. First of all, only half of the CAs approached responded. Therefore, the results may reflect practice of those CAs who are keen and active.

An online survey was a useful approach to gather responses from all around the country, but this may have put off some people who were internet shy. The survey was semi-structured from hospital specialist perspectives. Also, geographical breakdown of the respondents was not available. Although a further insight into CA practice was gained from free text of the survey a more comprehensive assessment could be undertaken using a qualitative approach, surveying not only CAs but also patients and hospital specialists in order to gain further knowledge of their practice and how best to support and integrate their service to achieve the best outcome for patients.

2.1.5 Conclusion

Continence advisors are an important part of the management of faecal incontinence. They are able to utilise many of the current treatments. There is room for improvement, and this may be achieved by focused and more easily accessible education.

3 Improving patient diagnosis and assessment with a new portable manometric device

3.1 Introduction

Anorectal physiology tests (ARP) provide a functional assessment of the anal canal and are considered part of the standard of care for patients with pelvic floor disorders (63). Currently, sphincteric assessment is performed with a combined approach of functional assessment with anorectal manometry and anatomical evaluation with an endo-anal ultrasound scan (see also Chapter 1.4) (54).

Manometric assessment is a key part of ARP and allows estimation of anal canal pressures, which are directly related to anal sphincter structure and function. Measurements include the anal canal resting pressure, maximum voluntary squeeze increment, involuntary squeeze increment, endurance squeeze / time and strain pressures (5,65,68,145).

In recent years, there has been much debate as to which type of device should be used to perform ARP measurements, with discussions focusing on improving the accuracy of ARP assessment (71). One of the traditional methods for anal manometry is the multi-channel water perfused catheters which take the average pressure at multiple intervals (71,146). Pressures are recorded after this catheter has been placed into the anorectum for a few minutes. Catheters range in size and channel position with the more recent manometry devices using a multi-channel water-perfused catheter able to record along both its longitudinal and radial axes. These catheters are durable and reliable, however their use, necessitates specific training and

they also require continuous maintenance. Developments in technology, however, have also produced solid state catheters and three-dimensional high definition manometry (147–151). These devices have a greater number of sensors per surface area, when compared with standard water perfused catheters. An additional benefit of this technology is that the topographical display produced by these newer devices may aid interpretation of ARP data. The main limitations of traditional solid-state catheters have been their cost and fragility (70,150).

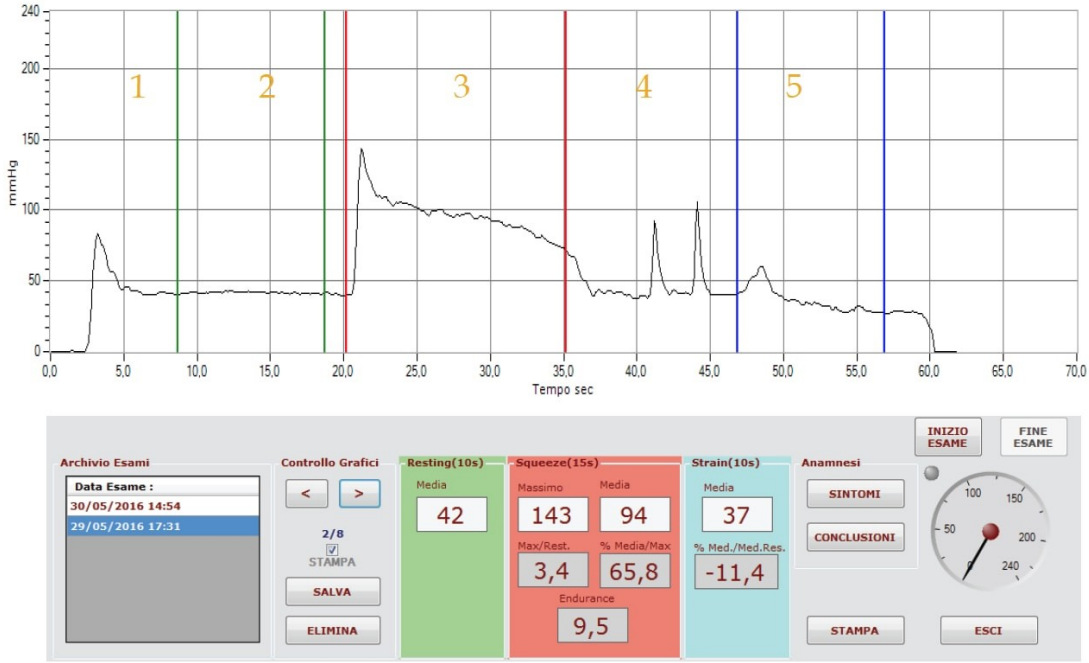
Anopress (THD Anopress, THD Worldwide, Correggio (RE), Italy) is a new portable anal manometry device (Fig. 3.1 and 3.2), which uses a new concept of air-filled catheter to evaluate the sphincter pressures generated from the whole of the anal canal (152). It has European Conformity (CE) and US Food and Drug Administration (FDA) approval. It has been promoted as a small, portable, wireless, reliable device that can perform rapid manometric assessments outside the anorectal physiology laboratory.

Despite this device being sold for clinical use there are no normative values for this new technology. The utility of this device in routine clinical practice in detecting anorectal dysfunction has also not been investigated. Furthermore, it is not possible to compare results from this device with other machines to determine how the Anopress compares with more established ARP devices.

Therefore, the aims of this chapter were: 1.) produce normative values for this new device by assessing a group of asymptomatic volunteers; 2.) evaluate the Anopress in clinical practice; and, 3.) compare the Anopress to standard water perfused manometry (WPM).

Figure 3. 1: The Anopress device is shown here with a laptop computer and the air-filled catheter connected. Bluetooth technology allows the Anopress device to work wirelessly. (THD SpA, 2017. Used with permission).

Figure 3. 2: The graph and figures as they appear on the Anopress display. This specific frame follows the protocol described in Chapter 2.2.2. Column labelled No 1 shows the anal cutaneous reflex. No 2 shows the resting pressure. No 3 shows the maximum voluntary squeeze pressure and endurance in a 15 seconds frame. No 4 shows two involuntary squeeze pressures and finally No 5 shows the straining pressure.



3.2 Method

3.2.1 Technique

The Anopress device (THD Anopress, THD Worldwide, Correggio (RE), Italy) (133) can communicate with any laptop computer via a Bluetooth connection. The single use air-filled catheter provided with the device must first be connected. This is achieved by rotating the catheter clockwise into the Anopress device connector. The catheters are made from latex free PVC, they are 15 mm in diameter, and have a single transduction area 5 cm in length on their radial surface. The transduction area is an air-filled space which transmits any pressure modification imposed onto the catheter. These pressure modifications are recorded every tenth of a second for the duration of the examination. The device is calibrated automatically by pushing the start button. This phase of the procedure takes approximately 10 seconds. The patient is positioned on the examination couch in the standard left lateral position. The catheter is lubricated and inserted gently into the anal canal until the area of the probe is in contact with the entire surface of the anal canal. The probe records the real time mean pressure of that entire area, which represents the radial forces generated by the whole sphincter complex. The device has three buttons that record specific phases of the procedure: resting pressure (green button), squeeze pressure (red button), and strain pressure (blue button). Subjects are initially asked to relax to allow the anal resting pressure to be measured until a stable trace is achieved which is then recorded for ten seconds. Following this, the patient is asked to squeeze as hard and long as possible to measure the maximum anal squeeze pressure and the anal endurance pressure over a period of 15 seconds. Involuntary squeeze pressures are measured by asking the patient to cough. Finally, subjects are asked to bear down, or to strain for 10 seconds, in order to simulate defecation (Fig. 4.2-4.3). At this point, the catheter is removed, and the data generated

by the procedure are immediately available for analysis using the laptop computer and can be edited accordingly.

A detailed video of this technique is available at the following link:

http://www.jnmjournal.org/journal/view.html?doi=10.5056/jnm17135

3.2.2 Normative values of Anopress

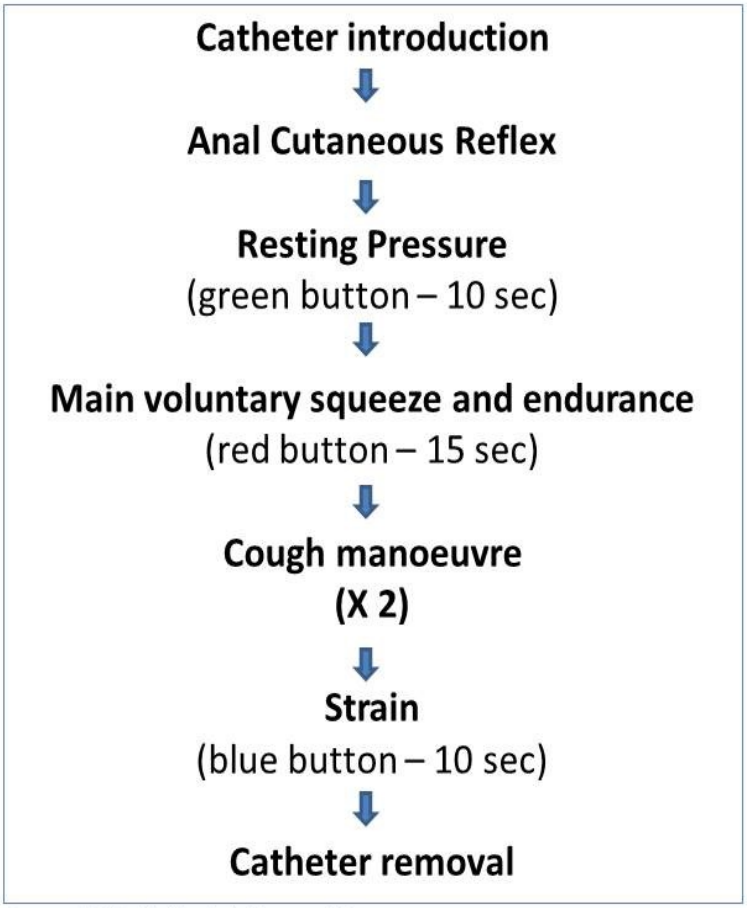
The Anopress device was used to assess asymptomatic volunteers. All subjects included in this study were recruited from the same centre. Institutional Review Board approval was granted (247/17; Modena Research Ethics Committee, University of Modena and Reggio Emilia, Italy). Ethical approval was gained in Italy as well as the recruitment of the subject. Extraction and analysis of the data was completed in the UK. Written consent was gained prior to subjects being included in the study. A full clinical history was taken prior to anorectal assessment. All subjects were selected excluding those with gastrointestinal symptoms and those who had any history of incontinence, constipation, anal pain, irritable bowel syndrome or inflammatory bowel disease were excluded. Subjects < 18 and > 80 year old were excluded.

All subjects were instructed to defecate if required prior to the procedure and no bowel preparation was given. Prior to the procedure it was confirmed that all subjects understood the commands squeeze, cough, and push prior to the procedure. Both genders were included in the study and the female cohort was subcategorised into nulliparous and parous groups. Anal resting, voluntary, involuntary, endurance, and strain pressures were determined as outlined in Fig. 3.3. The data generated by the procedure were automatically recorded and immediately available for review. All the values expressed by Anopress are summarized in Table 4.1. A

linear VAS score with the descriptor extremes “0 = no pain at all” and “10 = my pain is as bad as it could possibly be” was used to evaluate how comfortable patients found this new device.

Data are presented using either median values with interquartile range (25th-75th percentile) or normal range (2.5-97.5 percentile). Statistical analyses were performed using commercially available software (GraphPad Prism, Software Version 6, La Jolla, CA, USA). A p value < 0.05 was considered statistically significant.

Figure 3. 3: Study protocol for Anopress device: assessment of asymptomatic volunteers.



Leo et al. St Mark's Hospital, Harrow – UK.

3.2.3 Initial Evaluation of Anopress in patients with faecal incontinence

We reviewed prospectively collected data on adult patients with symptomatic faecal incontinence (FI) who had been assessed in the outpatient clinic using the Anopress device. All patients were examined in a single tertiary care specialist centre. Research and Development office approval was gained prior to data review (R&D No. SE16/039 London North West NHS Trust). A full clinical history had been taken, including the severity of FI estimation using the St Mark's FI score, for all patients prior to Anopress assessment. A standard protocol was followed for all patients: patients were instructed to defecate if required prior to the procedure and no bowel preparation was given. It was confirmed that all subjects understood the commands squeeze, cough and push prior to performing each procedure. Resting pressure, voluntary squeezes, involuntary squeezes (cough manoeuvre) and endurance pressure increments were recorded in keeping with a previous published protocol. Endurance was defined as the progressive duration of contraction of up to 50% of the maximum squeeze pressure, and as a value expressed in mmHg at a maximum of ten seconds. The data generated by this investigation had been recorded for each patient using the Anopress device. A visual analogue scale (VAS) pain score had been recorded for all patients during this test with the descriptor extremes "0 = no pain at all" and "10 = my pain is as bad as it could possibly be" to evaluate how comfortable patients found this new device.

Descriptive statistics are presented using median and range values. The Mann-Witney-U test was used to analyse the study data using commercially available software (GraphPad Prism Software Version 6, La Jolla, CA, USA). A p value < 0.05 was considered statistically significant.

3.2.4 Comparing Anopress to the standard water perfused manometry (WPM)

This prospective observational study to compare these two technologies had received a Health Research Authority approval by the London – Dulwich Research Ethics Committee prior to initiation (16/LO/1577). The study protocol was registered with the NHS National Health Research Authority under IRAS ID 207753.

3.2.4.1 Outcome measures

Primary outcome measures:

- To compare the manometric values obtained by two different manometric technologies.

Secondary outcome measures:

- To compare patients device tolerability.
- To describe a qualitative analysis of the two devices and their relative catheters.

3.2.4.2 Patients

The study was performed in the Sir Alan Park's Physiology Unit of St Mark's Hospital London, in the United Kingdom. Adult patients who were referred for anorectal physiology studies because of faecal incontinence in accordance with national guidelines were eligible for inclusion. Those referred for other reasons such as anal pain, irritable bowel syndrome and inflammatory bowel diseases were excluded from this study. Patients were approached and informed about the study in the anorectal physiology clinic by the doctor performing the tests. Full informed consent was gained prior to the tests. If patients declined or could not be included in this study, they were offered anorectal physiology tests according to the current standard of care. We aimed to include 60 male and female patients in a 1:1 ratio for reasons of comparison

between genders. This group of patients was different from those recruited from previous studies.

3.2.4.3 Anorectal physiology studies

Prior to the procedure, patients were instructed to defecate if required and no bowel preparation was given. Investigators confirmed that all subjects understood the commands squeeze, cough, and push prior to the procedures. All investigations were performed in the left lateral position in the presence of a chaperone. The manometric investigations were performed consecutively in the same clinic session. Patients were randomized with sealed envelope methodology which determined the technology that was used first. All the standard manometry manoeuvres were performed according to the study protocols. After positioning of the catheter, a period of 5 minutes was taken to allow for a resting pressure to be measured. Following this the maximum voluntary squeeze pressure, 5 second endurance, maximum involuntary squeeze and strain pressure were measured. Each manoeuvre was performed twice with a 30 second interval between each step of the protocol.

3.2.4.4 Water perfused anorectal manometry

Single use water perfused catheters were used with a diameter of 4.9 mm and 10 channels spaced at 8 mm intervals between 0 and 7.2 cm distance of the tip (Fig. 3.4 - A). The channels were connected to external pressure transducers. These convert the recorded pressures to a high resolution colour plot displayed on the monitor of a solar MMS manometry system with High Resolution software (Medical Measurements Systems, Enschede, The Netherlands version 9.5) (27) (Fig. 3.4 - B). Prior to each test, the catheters were infused with physiological solution (about 200 ml) and calibrated as for standard technique. The catheter was inserted into the anus

to about 10 cm from the anal verge and advanced slowly until the balloon on the distal end of the catheter was in the rectum. This is represented on the display screen by a low-pressure zone. A higher-pressure zone representing the anal canal was seen in the centre of the graph and a further lower pressure zone representing the channels outside of the body was seen on the monitor (Fig. 3.4 - C). Normal values used in clinic for this device are shown in Table 3.1.

3.2.4.5 THD® Anopress

Single use air filled catheters (THD PressProbe ENV, Figure 3.5) measure the average pressure of the whole anal canal at once. This is achieved by a toroidal membrane in direct contact with the anal canal on one side and a pressure transducer on the other side. These allow pneumatic pressure measurements without the need of a sensor on the surface of the probe. These probes are 17 cm in length, including 8 cm of pneumatic membrane and have a maximum diameter of 15 mm. The catheter was calibrated prior to each test by allowing the air-filled catheter to record the ambient atmospheric pressure. The catheter was then inserted into the anus for the entire length of the device. A minimum of 5 minutes was used to stabilise the pressure. Then the same manoeuvres were repeated as above for the WPM according to the study protocol. Normal values used in clinic for this device were the result of the previous study and these are shown in Table 3.2 (see also Chapter 3.3.1).

Table 3. 1: Normal values used in the Sir Alan Park's Physiology Unit (St Mark's Hospital) for water perfused manometry.

WPM (cmH_20)	**Female**	**Male**
Maximum resting pressure	60 – 160	60 – 160
Maximum squeeze increment	50 – 180	60 – 220
Involuntary squeeze increment	50 – 100	50 – 100
Five seconds squeeze increment	40 – 160	40 – 200

Table 3. 2: Normal values used in the Sir Alan Park's Physiology Unit (St Mark's Hospital) for the THD® Anopress (see also Chapter 4.3.1).

THD® Anopress (mmHg)	**Female**	**Male**
Maximum resting pressure	40 – 103	38 – 99
Maximum squeeze increment	35 – 140	42 – 155
Involuntary squeeze increment	41 – 120	40 – 123
Ten seconds squeeze increment	44 – 98	43 – 103

Figure 3. 4: Water perfused High Resolution Manometric manometry uses: a.) water perfused catheter; b.) hardware device used in our centre for manometry; and, c.) pressures as they appear on the monitor using the High-Resolution Manometry.

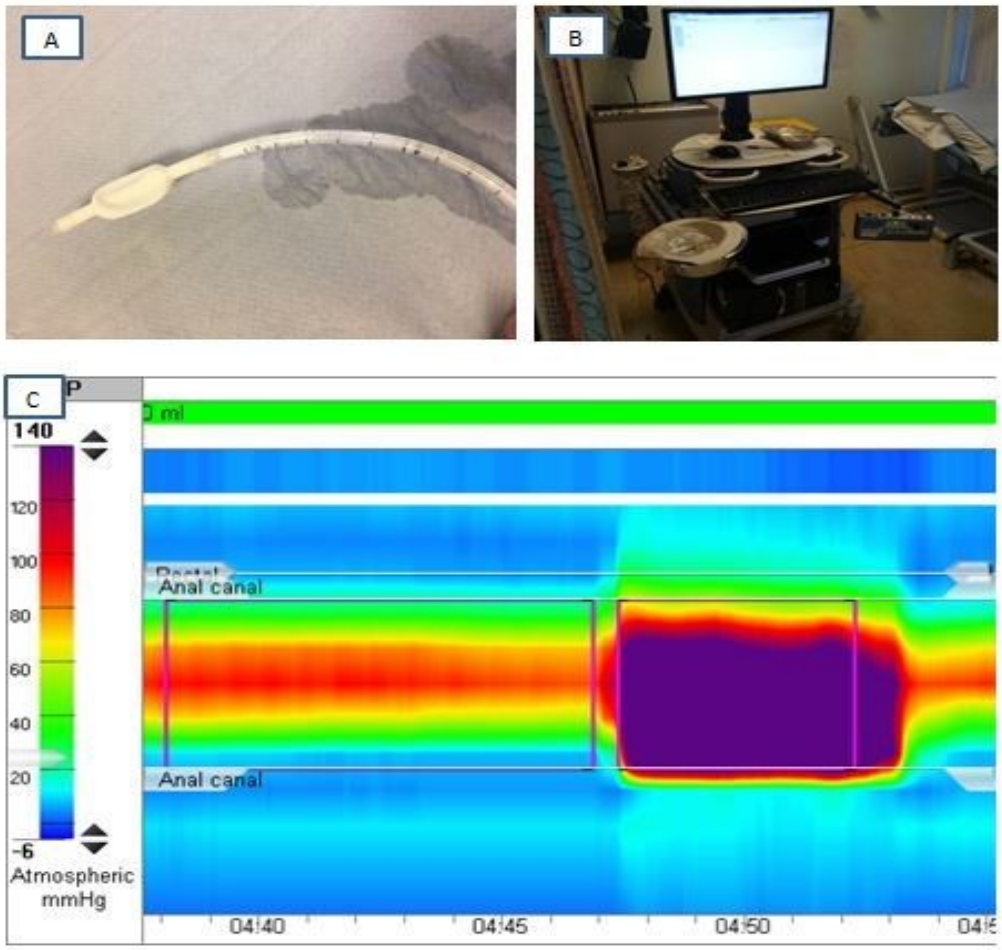
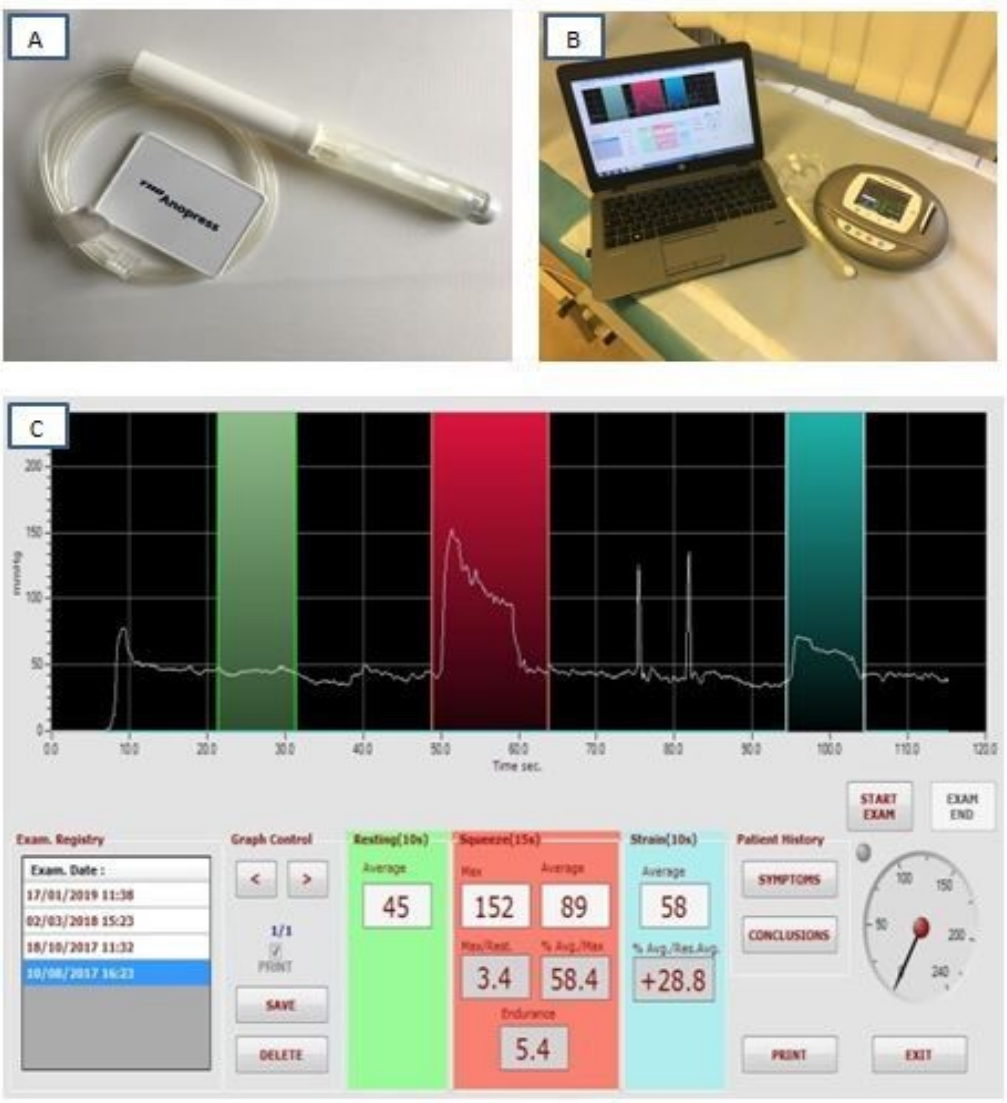


Figure 3. 5: THD® Anopress uses the: a.) air-filled catheters; b.) portable hardware device used for this study; and, c.) pressure graphs as they appear on the Anopress screen.



3.2.4.6 Data collection

The data that were prospectively recorded included the patient's medical history, physical examination and laboratory findings all of which were entered on a structured case record form as per standard care. St Mark's faecal incontinence scores were obtained for all participants to allow objective measurement of the symptom severity. A visual analogue scale (VAS) with "0 = no pain at all" and "10 = my pain is as bad as it could possibly be" was used at both insertion and during the procedures. The time taken for the resting pressure to stabilise, maximum anal resting pressure, main voluntary squeeze increment (difference between the maximum voluntary squeeze pressure and the maximum resting pressure), endurance squeeze for 5 seconds (increased average pressure within 5 seconds of maximum squeeze pressure), involuntary squeeze pressures and straining pressures for both tests were recorded.

3.2.4.7 Statistical analysis

The resting and squeeze pressures were summarised by giving the mean and standard deviation if normally distributed, and the median with interquartile range if not normally distributed. The aim of the analysis was to compare patient outcomes between the two test methods. For variables where the values were known to vary between methods, the analyses examined the strength of association between the patient outcomes of WPM and Anopress.

Pearson correlation was used for normally distributed variables, whilst Spearman's rank correlation was used for variables that were not normally distributed. The use of correlation was the most appropriate methodology due to objective differences in the two devices and because it was not anticipated that the same values would be generated by both devices for each participant. The results were displayed graphically using scatterplots. For other variables,

the difference in values between the devices was examined. Due to the repeated measurements per participant (one per method), the analyses were performed using multilevel regression methodology. Multilevel linear regression was used for continuous outcomes, whilst multilevel logistic regression was used for binary outcomes. The models included terms for the order in which the tests were performed, and the methods used continuous outcomes found to exhibit a positively skewed distribution were given a log transformation before analysis. For the VAS score at insertion, a small constant of 1 was added before transformation, as it was not possible to log transform zero values which were found for this variable.

Also, for completeness of the study, the Bland-Altman plot has been used to assess the repeatability of the method by comparing repeated measurements using one single method on this series of subjects. Unit were also converted and standardised from cmH2O to mmHg and statistical analysis was repeated to see whether there were any difference in the comparison between the two series of manometric results.

P values of < 0.05 were considered statistically significant. All analyses were performed using the software package Stata (version 15.1). Statistical methodology was designed and undertaken by a professional medical statistician.

3.2.4.8 Qualitative analysis

A description of the qualitative properties of both devices and catheters was undertaken. This took the form of a descriptive report and compared both technologies in an objective fashion.

3.3 Results

3.3.1 Normative values of Anopress

Between April 2016 and June 2017, 153 asymptomatic subjects were recruited, 80 (53.3%) of whom were female. The median age was 39.5 (IQR, 28.75-53.00) and 40.5 (IQR, 29.00-52.25) years of age in the female and male groups, respectively. Of the female cohort, 23 were parous and the median age was 40 (range, 19-79).

Normal range (2.5-97.5 percentile) values were recorded across the whole anal canal for both female and male patients. The calculated normal anal resting pressure ranges were 40.0-103.0 mmHg in the female group and 38.3-99.6 mmHg in the male group. Normal range values for maximum squeeze increment were 35.0-140.6 mmHg in the female and 42.5-154.8 mmHg in the male subject groups. Normal values for endurance squeeze were calculated as 1.3-9.0 seconds in the female and 2.0-10.0 seconds in the male groups. The normal range for involuntary maximum squeeze was 41.1-120.8 mmHg in the female group and 40.0-123.6 mmHg in the male group. Finally, normal range strain pressures were 22.1-77.9 mmHg and 11.0-72.1 mmHg respectively in the female and male cohorts. Normal range values for Anopress assessment in all groups are summarized in Table 4.2.

When the male and female groups were compared, a statistically significant difference was noted for anal resting pressure ($p = 0.044$), squeeze increment ($p < 0.001$) and endurance squeeze pressures ($p = 0.042$). When nulliparous and parous female cohorts were compared a statistically significant difference was noted for anal resting pressure ($p = 0.026$). Results of the statistical analysis are outlined in Table 3.3.

All subjects tolerated the procedure without significant discomfort and a median VAS score of 0 (IQR, 0.00-0.00) was recorded for all study subjects. No complications occurred during the study. In all cases the probe was placed once and did not need to be repositioned for the appropriate measurements to be taken.

Table 3. 3: Pressures expressed using either median values with interquartile range or 2.5 - 97.5 percentile ranges for a cohort of 153 asymptomatic volunteers. Mann-Whitney U analysis was used to analyse differences between male and female groups and between nulliparous and parous female groups. * indicates a p value < 0.05.

	Asymptomatic volunteers				
	Female		**Male**		**P values**
	median (IQR)	normal range	median (IQR)	normal range	
Resting pressure (mmHg)	67 (54.8-79.0)	40.0 - 103.0	61.8 (54.8 – 79.0)	38.3 - 99.6	$p = 0.044$*
Squeeze increment (mmHg)	75.5 (54.5-98.0)	35.0 – 140.6	101.0 (86.0 – 121.0)	42.5 – 154.8	$p < 0.001$*
Involuntary sq. (mmHg)	69.5 (55.0 – 98.0)	41.1 - 120.8	79 (56.0 – 99.0)	40.0 - 123.6	$p = 0.236$
Endurance (sec.)	4.5 (4.0 – 5.1)	1.3 - 9.0	5.0 (4.0 – 6.3)	2.0 - 10.0	$p = 0.042$*
Strain (mmHg)	43.5 (31.0 – 54.3)	22.1 - 77.9	45.2 (32.0 – 55.0)	11.0 - 72.1	$p = 0.564$

	Female asymptomatic volunteers				
	Nulliparous		**Parous**		
	median (IQR)	normal range	median (IQR)	normal range	
Resting pressure (mmHg)	61.0 (54.0 – 78.0)	39.5 - 102.1	75.0 (67.0 - 84.5)	41.0 - 105.0	$p = 0.026$*
Squeeze increment (mmHg)	75.0 (57.0 – 95.0)	30.5 - 137.0	83 (53.0 – 102.0)	35.0 – 141.0	$p = 0.468$
Involuntary sq. (mmHg)	76.0 (55.0 – 98.0)	41.0 - 135.3	65.0 (55.0 – 87.0)	45.0 - 110.0	$p = 0.311$
Endurance (sec.)	4.5 (4.0 – 5.1)	1.2 - 9.1	4.1 (3.8 - 5.1)	2.9 - 7.0	$p = 0.464$
Strain (mmHg)	41.0 (31.0 – 54.0)	23.4 - 75.3	50.0 (43.0 - 55.5)	21.0 - 78.0	$p = 0.053$

3.3.2 Initial evaluation of Anopress in patients with faecal incontinence

Between June 2016 and June 2017, 60 patients with symptomatic FI underwent assessment using the Anopress device. Of these, 45 (75%) were female. The median (range) age was 51 (21 – 88) years for females and 61 (22 - 87) years for males respectively.

The predominant symptom was a combination of urge and passive FI in 34 (57%) patients, urge FI was found in 18 (30%) patients and the remaining 8 (13%) patients had pure passive FI. The median St Marks FI score was 15 (7 – 24) in females and 11 (9 – 24) in males respectively.

Resting pressures were 25 (0 - 60) mmHg in the female group and 30 (0 – 52) mmHg in the male group. Maximum squeeze increments were 27 (6 - 106) mmHg in the female and 42 (6 - 99) mmHg in male groups. Endurance squeeze increments were 3.9 (0.4 - 10) seconds in the female and 3.3 (0.3 – 4.3) seconds in the male groups. Maximum endurance at 10 seconds was 32 (5 – 89) mmHg in the female group and 31 (10 - 65) mmHg in the male group. Involuntary maximum squeeze pressures were 33 (6 – 103) mmHg in the female group and 27 (7 - 90) mmHg in the male group. Recorded measures are shown in Table 4.4. These results were compared to normal values in Chapter 4.3.1. A statistically significant (p<0.05) reduction in all pressure measurements was seen (Table 3.4). Patients with higher incontinence scores had lower manometric results as expected.

The procedure was well tolerated by all patients with a median VAS pain score of 0 (0 – 2) during insertion and 0 (0 – 1) during the procedure.

Table 3. 4: Demographic details and manometric parameters recorded in the cohort of 60 patients symptomatic for faecal incontinence. Parameters are expressed in median and range. Pressures are expressed in mmHg. NC = Not Compared. SMIS = St Mark's incontinence score.

	Female symptomatic (No. 45)	**Female Normal values**	***p* value**	**Male symptomatic (No. 15)**	**Male Normal values**	***p* value**
Age	51 (21 – 88)	39.5 (19 – 79)	NC	61 (22 – 87)	41 (18 – 74)	NC
SMIS	15 (7 – 24)	0	< 0.05	11 (9 – 24)	0	< 0.05
Resting Pressure	25 (0 - 60)	40.0 - 103.0	< 0.05	30 (0 - 52)	38.3 - 99.6	< 0.05
Max Squeeze Increment	27 (6 - 106)	35.0 – 140.6	< 0.05	42 (6 - 99)	42.5 – 154.8	< 0.05
Endurance in mmHg	32 (5 - 89)	44 - 98	< 0.05	31 (10 - 65)	43 - 103	< 0.05
Endurance in sec	3.9 (0.4 - 10)	1.3 - 9.0	< 0.05	3.3 (0.3 – 4.3)	2.0 - 10.0	< 0.05
Involuntary Squeeze	33 (6 - 103)	41.1 - 120.8	< 0.05	27 (7 - 90)	40.0 - 123.6	< 0.05

3.3.3 Comparing Anopress to the standard water perfused manometry (WPM)

Between December 2016 and June 2017, 60 patients were recruited (30 male and 30 female) from the Sir Alan Park's Physiology Unit at St Mark's Hospital, UK. Their mean age was 58.6 years (SD 12.2). The mean St Marks FI score was 14.6 out of 24 (SD 5.9). All patients received both tests. In 30 patients the WPM was performed first, and for the other 30 patients THD Anopress was performed first (Table 3.5). No complications or side effects were recorded during or after either test. The anorectal contractile reflex was observed in all with both tests. No difference was noted for this reflex.

Table 3. 5: Patient demographics and baseline characteristics. Summary statistics are: number (percentage) or mean ± standard deviation.

Variable	Category	Summary
Age	-	58.6 ± 12.2
Gender	Male Female	30 (50%) 30 (50%)
Test order	WP first THD first	30 (50%) 30 (50%)
St. Mark's score	-	14.6 ± 5.9

3.3.3.1 Manometric values

The median time from insertion of the catheter to the arrival at the resting pressure plateau was significantly lower with the Anopress compared to WPM; 12 seconds (IQR 10 to 17 seconds) and 100 seconds (IQR 67 to 121 seconds, $p < 0.001$ respectively). The WPM had a mean resting pressure of 44.3 cmH2O (± 15.8 SD), median voluntary squeeze increment of 57 cmH2O (IQR 31 to 102), the mean squeeze endurance at 5 seconds was 43.7 cmH2O (± 39.3 SD), the mean involuntary squeeze increment of 54.3 cmH2O (± 33.1 SD) and a straining pressure of 20 cmH2O (IQR of 10 to 42). In comparison, the Anopress had a mean resting pressure of 37.5 mmHg (± 17.0 standard deviation), median voluntary squeeze increment of 64 mmHg (IQR of 29 to 101), the mean squeeze endurance at 5 seconds was 44.7 mmHg (± 35.1 SD), a mean involuntary squeeze increment of 61.0 mmHg (± 35.7 SD) and a straining pressure of 21 mmHg (IQR of 11 to 45). The r^2 correlation coefficients showed a strong positive association between the WPM and the Anopress measurements. These were 0.84 for resting pressure, 0.97 for voluntary squeeze increment, 0.90 for endurance of voluntary squeeze, 0.96 for involuntary squeeze increment, and 0.91 for strain pressure (all with $p < 0.001$). All manometric values are listed in Table 3.6 and the associations between WPM and the Anopress are shown in Figure 4.4.

Additionally, as part of the same analyses the differences in outcome were assessed between the two periods (first test vs. second test). The results suggested that none of the outcomes significantly varied between the two study periods. There were also no statistically significant differences in outcome when compared the results between the two genders.

Using the Bland – Altman analysis to compare the two measurements techniques there were no significant differences and the two methods can be considered to be in agreement and therefore may be used interchangeably. Graphical illustrations of these results are shown in Fig. 3.6 and 3.7.

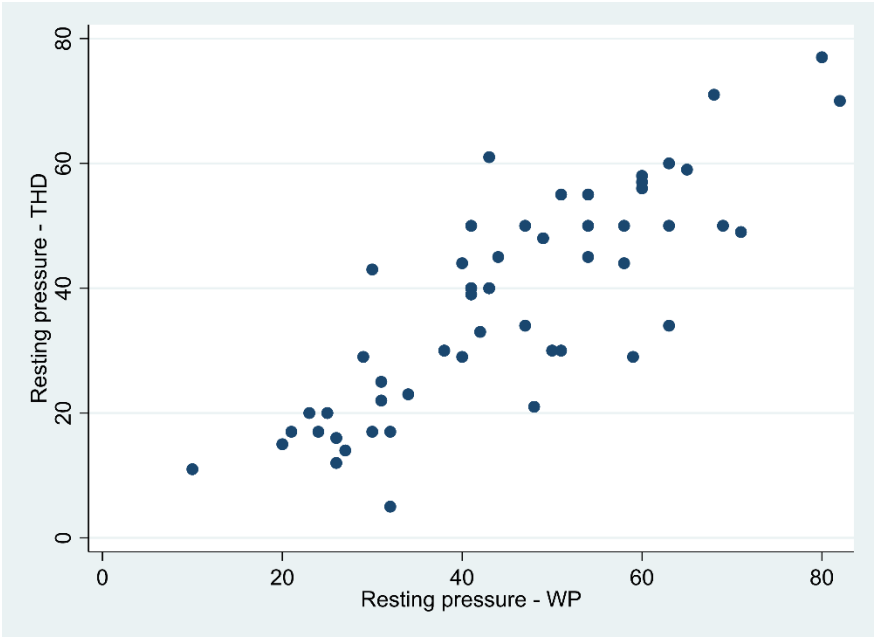
Also, when the unit where converted and standardised from cmH2O to mmHg and then compared to the first series of results there was no statistical significance, confirming a strong positive association between the WPM and the Anopress measurements.

Table 3. 6: Comparison of outcomes between methods, giving the median or mean and the correlation between measurements, and p values indicating the significance of the association.

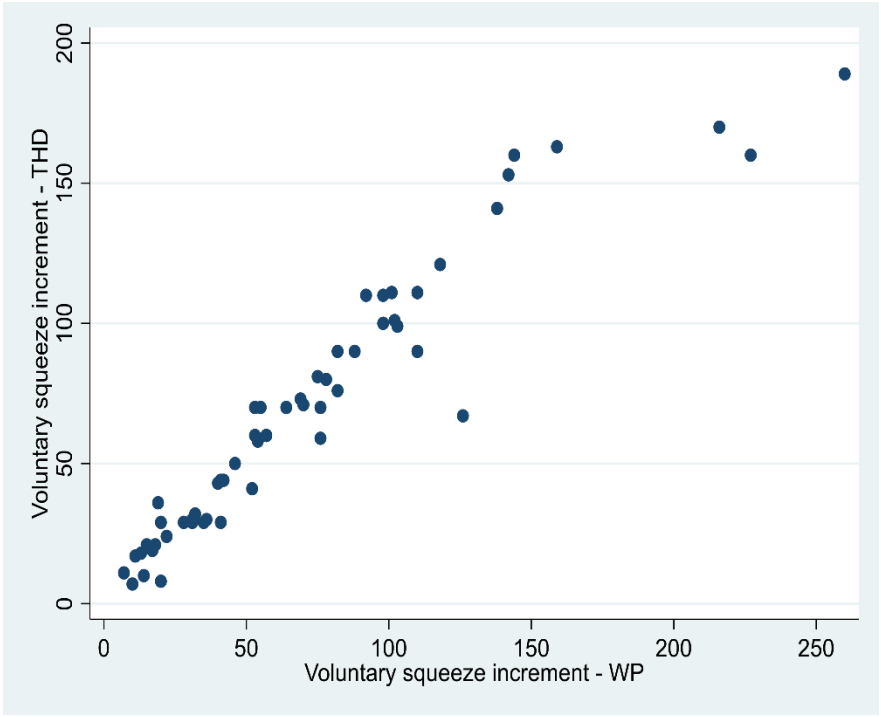
Measurement	**THD**	**WPM**	**Correlation coefficient**	***p* value**
Time to resting pressure	Median 12sec, IQR 10-17	Median 100 sec, IQR 67-121		
Resting pressure	Mean 37.5 mmHg ± 17.0 SD	Mean 44.3 cmH2O ± 15.8 SD	0.84*	<0.001
Voluntary squeeze increment	Median 64 mmHg IQR 29-101	Median 57 cmH2O, IQR 31-102	0.97**	<0.001
Endurance at 5 seconds	Mean 44.7 mmHg ± 35.1SD	Mean 43.7 cmH2O ± 39.3 SD	0.90**	<0.001
Involuntary squeeze increment	Mean 61.0 mmHg ± 35.7 SD	Mean 54.3 cmH2O ± 33.1 SD	0.96**	<0.001

Figure 3. 6: Graphical illustrations of the association between WPM and Anopress are shown for: **a.)** resting pressure measurements; **b.)** voluntary squeeze increment measurements; **c.)** endurance measurements; **d.)** involuntary squeeze increment measurements; and, **e.)** straining pressure.

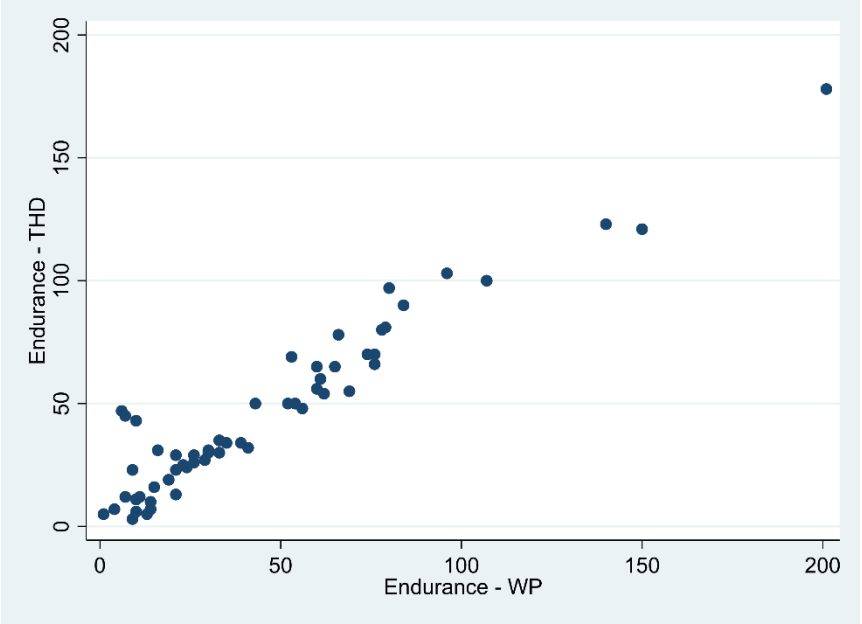
a.)



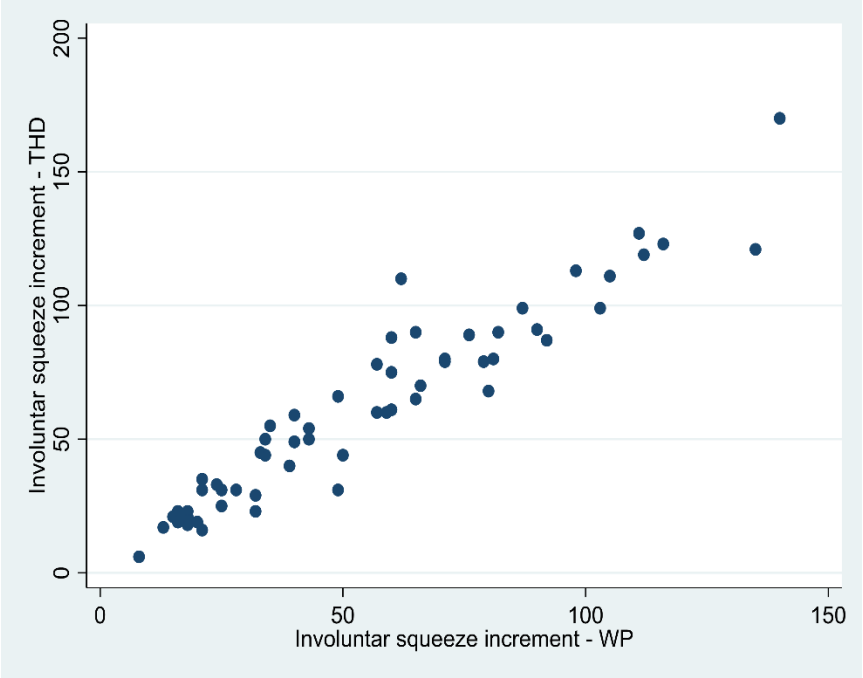
b.)


Voluntary squeeze increment - THD
0
50
100
150
200
0
50
100
150
200
250
Voluntary squeeze increment - WP

c.)


Endurance - THD
0
50
100
150
200
0
50
100
150
200
Endurance - WP

d.)


Involuntar squeeze increment - THD
0
50
100
150
200
0
50
100
150
Involuntar squeeze increment - WP

e.)

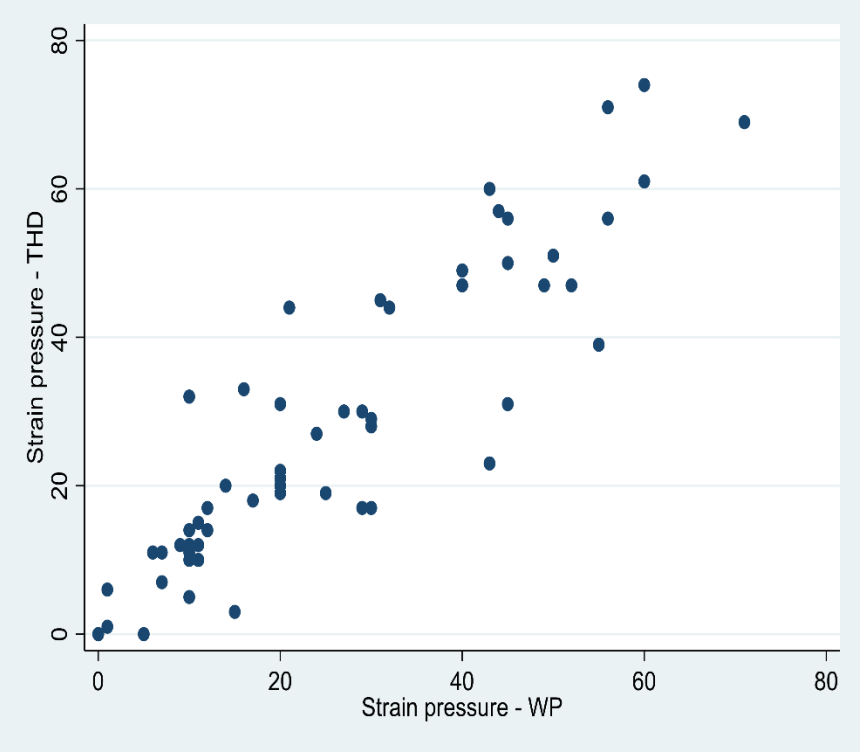
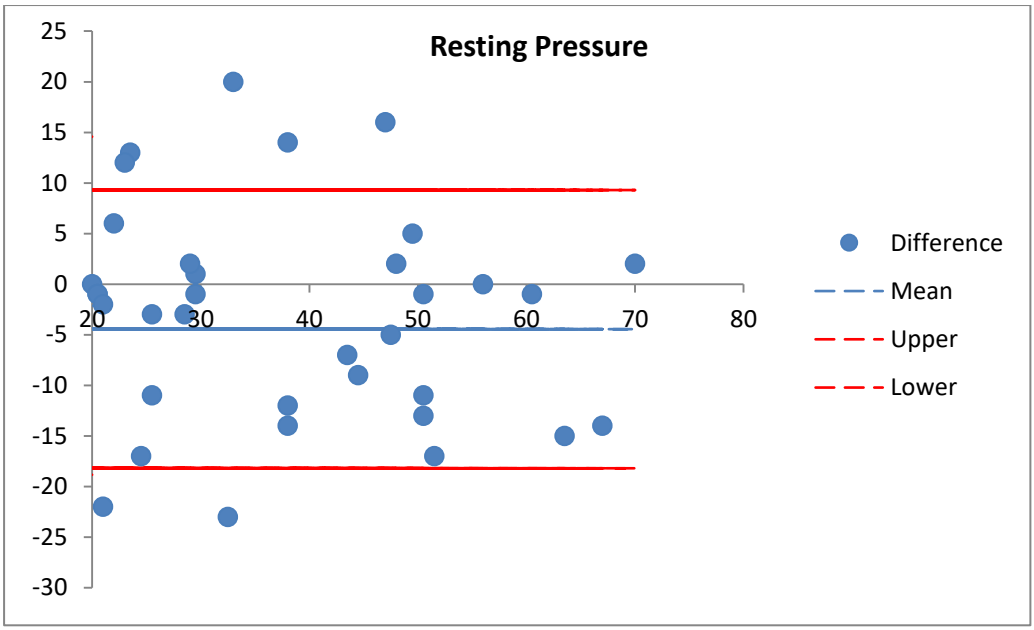
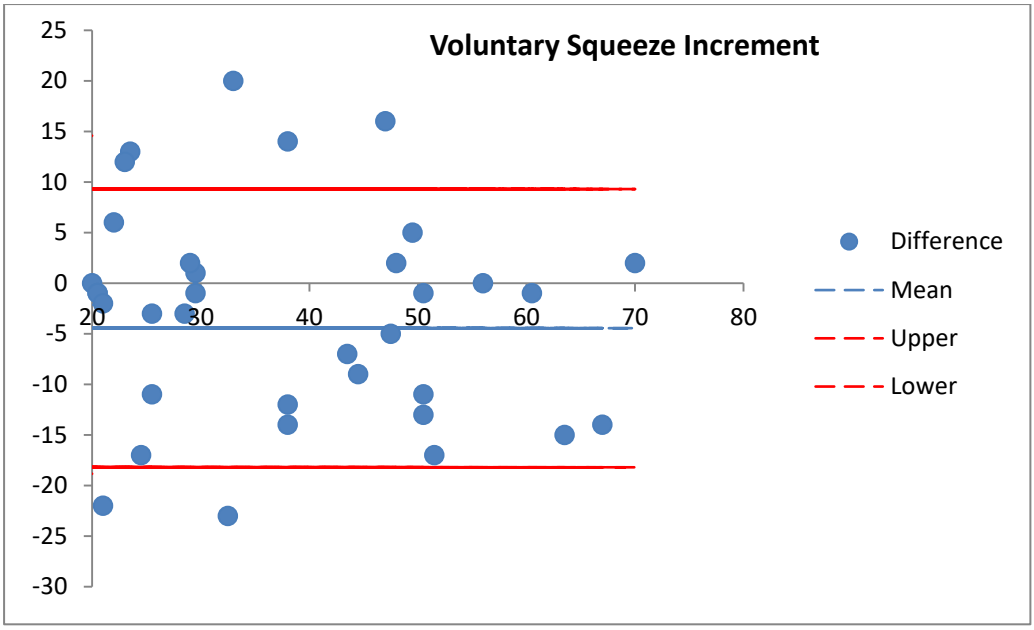

Strain pressure - THD
0
20
40
60
80
0
20
40
60
80
Strain pressure - WP

Figure 3. 7: Illustrations of the Bland – Altman analysis to compare the two measurements techniques. In this graphical method the differences between the two techniques are plotted against the averages of the two techniques (WPM and Anopress) with a 95% confidence interval of the Limits of Agreement (LoA): **a.)** resting pressure measurements; **b.)** voluntary squeeze increment measurements; **c.)** endurance measurements; **d.)** involuntary squeeze increment measurements; and, **e.)** straining pressure.

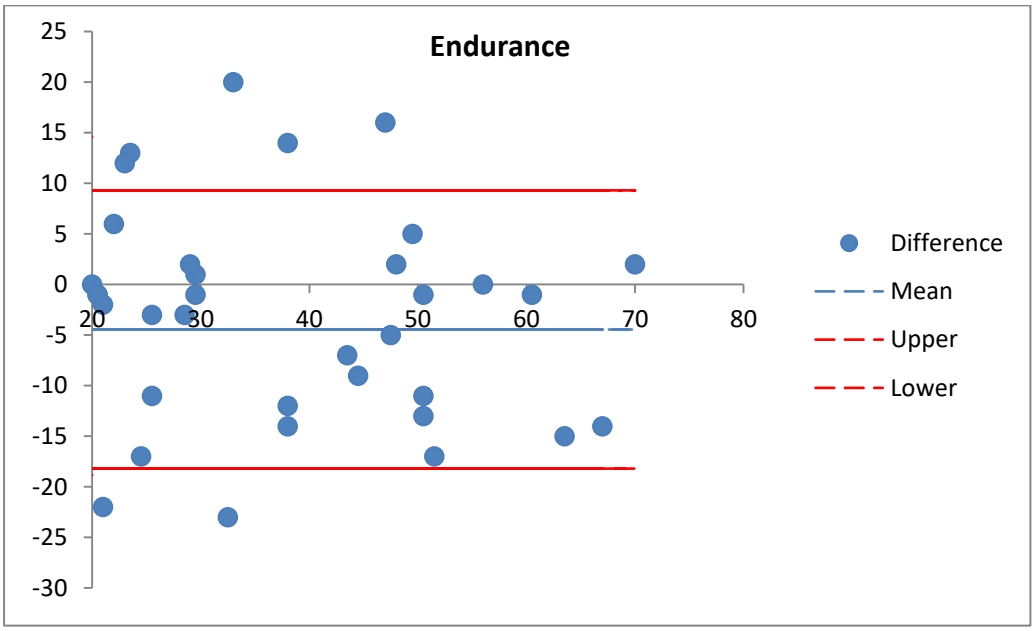
a.)



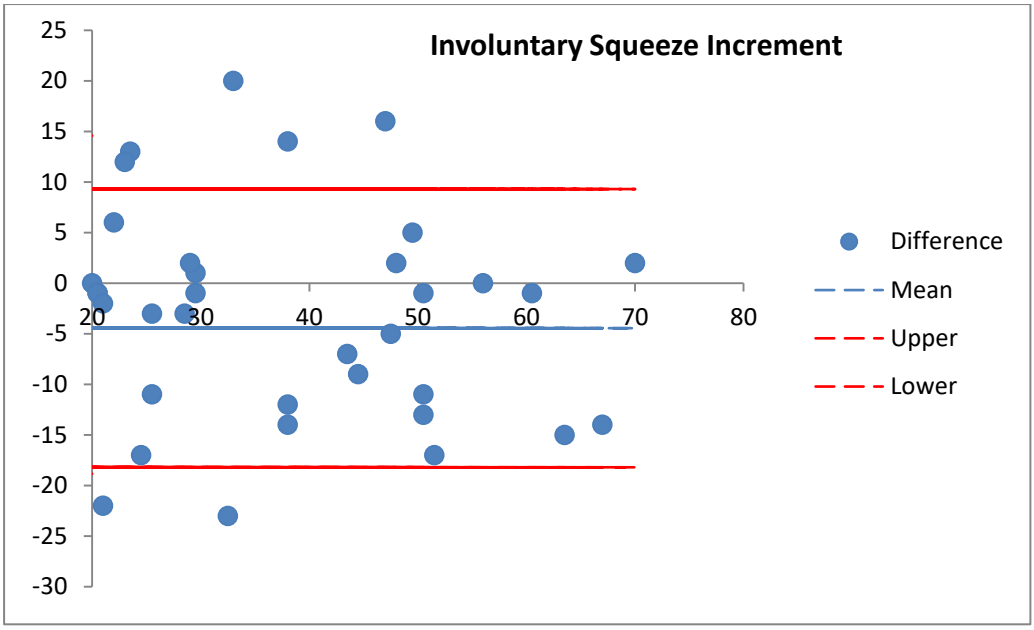
b.)


Voluntary Squeeze Increment
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
20
30
40
50
60
70
80
Difference
Mean
Upper
Lower

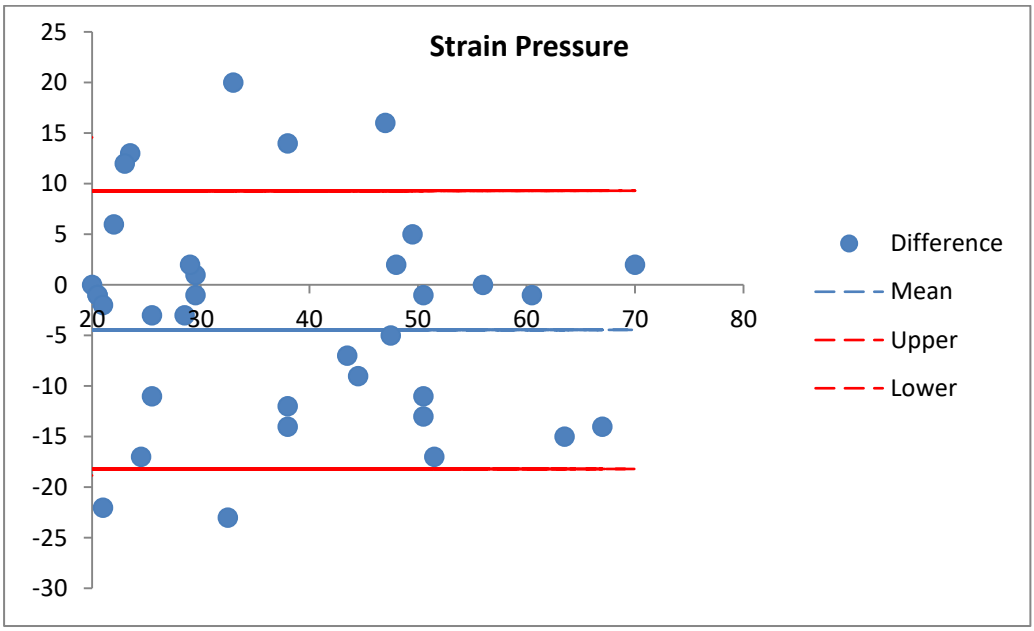
c.)


Endurance
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
20
30
40
50
60
70
80
Difference
Mean
Upper
Lower

d.)


Involuntary Squeeze Increment
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
20
30
40
50
60
70
80
Difference
Mean
Upper
Lower

e.)


Strain Pressure
25
20
15
10
5
0
-5
-10
-15
-20
-25
-30
20
30
40
50
60
70
80
Difference
Mean
Upper
Lower

3.3.3.2 Patient device tolerability

The median VAS at introduction of the catheter at the WPM test was significantly higher (VAS of 2, IQR 1 – 5) compared to the Anopress, which had a median VAS of 0 (IQR 0 – 1, $p < 0.001$). The procedure was tolerated well for both groups. The VAS was mostly zero scores for both techniques (Median 0, Range 0 – 2). Eleven out of 60 (18%) patients reported discomfort during the WPM test with a VAS higher than 1. Seven out of 60 (11%) reported discomfort during the THD® Anopress test ($p = 0.31$).

3.3.3.3 Qualitative analysis

Details of the qualitative analysis are listed in Table 3.7 and 3.8. The WPM is heavy and bulky compared to the Anopress. The latter is portable, so it is easier to use compared to WPM when the help of an assistant is lacking. The Anopress catheter requires a maximum of 10 seconds to calibrate. This is an advantage when compared to the greater length of time needed to calibrate the catheter of the WPM (about 5 minutes). The WPM catheters used are thinner (4.9 mm), but long and floppy. They require that the catheter is passed into the rectum to allow the channels to gain position in the anal canal. The Anopress probes are slightly thicker (15 mm) but are ergonomic and have a smoother surface. They simply require passage into the anal canal to achieve a correct position. Conversely, the WPM allows measurement of the anal canal length and has integrated rectal balloon tests, both of which are not possible with the Anopress probes used for this study. Also the WPM has the advantage to allow vector volume measurements.

Table 3. 7: A qualitative analysis of the two devices: THD and WPM. *Note: volume and size are approximate and include their own station. **Note: cost comparison is based on the UK market. This may vary from country to country and from order volume. The price indicated by the two companies is £ 4950 (Anopress device) vs £ 18000 WPM device.

	WPM	**THD® Anopress**
Main device		
Weight and size*	> 10 kg, 100 x 150 cm	< 1 kg, 30 x 30 cm
Connection	Wired	Wireless
Mobility	Stationary	Portable
Software	High Resolution	Coloured single trace
Reading	Standard	Very easy
Cost**	£ 18000	£ 4950

Table 3. 8: A qualitative analysis of the two catheters used for this study. *Note: cost comparison is based on the UK market. This may vary from country to country and from order volume. The price indicated by the two companies is £ 22.00 for the Anopress catheters vs £ 50 – 60 for the WPM catheters.

Catheter		
Technology	Water Perfused	Air Filled
Preparation	Time consuming	Easy
Calibration	5 to 10 seconds	3 to 5 minutes
Sensors	Ten spaced sensors	Pneumatically membrane
Technique	Stationary	Pull-through examination
Position	Anorectum	Anal canal
Length of the anus	Accurate	NA
Balloon tests	Possible	NA
Vector volumes measurements	Possible	NA
Test lifespan	Long	Short
Cost*	£50	£22

3.4 Discussion

The initial study was designed to obtain the first normative values for the new Anopress manometry device, which have been presented above. This study is also one of the largest reported groups in the published literature describing normal values for anal manometry in asymptomatic subjects, irrespective of the technology used. As part of this work it was also determined how tolerable patients found Anopress assessment, with all subjects reporting minimal discomfort.

The subjects recruited to this study were a heterogeneous cohort of male and female (both nulliparous and parous) subjects. This heterogeneity was explicitly sought in order to generate normal values that would be applicable for disparate groups of patients in future. As expected, and as already reported by previous studies for different manometry devices, differences were observed between the subgroups of our study cohort. Specifically, significant differences were observed in resting pressures, squeeze increment and endurance pressures when comparing male and female subjects, contributed to by the longer anal canal in men. The significant difference seen in resting pressures noted when comparing parous and nulliparous women is likely to be a consequence of unidentified and asymptomatic sphincteric lesions caused by obstetric injury. Consequently, the nulliparous female group should be considered the true normative values, as the parous group are potentially an asymptomatic cohort at present who may go on to develop functional problems in future, rather than a group of truly asymptomatic healthy volunteers.

When comparing the presented results with the published literature the normative values for Anopress are lower than values used for water perfused manometry and previously validated

high-resolution manometry values (153). The data presented in this chapter are in keeping with previous published reports assessing another portable manometry device (Medspira, Minneapolis, MN, USA) (150). However, published data assessing this device are limited given one of these studies assessed only a small cohort as the authors aim was to validate pressure measurements rather than report normative values. The lower normal values reported by this chapter and those assessing the Medspira device are due to differences in the technologies used by these portable devices, which record values from the whole of the anal canal rather than the maximum values along the length of the canal as is the case for other devices.

In the second study presented in this chapter, statistically significant reductions in all of the measured parameters in patients with symptomatic FI were demonstrated, which indicates that the Anopress device is able to detect impaired sphincter function in those with symptomatic FI. The major objective advantages of this device that were observed include the ease with which it can be calibrated in only a few seconds, the fact that water perfusion is not necessary and the minimal effort required to position the catheter. Also this device once again appeared to be well tolerated by the patients, as demonstrated by the median VAS scores of zero during both insertion and assessment. An important limitation for this study was the small cohort of patients, consequently the lack of heterogeneity of the group and the impossibility to perform a correlation statistical analysis.

The third and final study was a prospective observational analysis that demonstrated a strong correlation between the manometric measurements of the current standard of care high-resolution water perfused manometry and the newer Anopress. The Anopress arrived at the

resting pressure plateau significantly faster than the water perfused catheter and the qualitative analysis shows that the Anopress may have also overcome many of the disadvantages of water perfused manometry.

Firstly, the Anopress is smaller, lighter, portable and wireless, and is more user friendly than WPM due to the integration between the device and the computer interface. Secondly, the preparation and calibration of the catheter is easier and faster. Furthermore, the Anopress catheters are less expensive than the WPM catheters. Anopress single line plot manometry may be easier to read, which makes it simpler to train staff in performing these investigations. The Anopress measures the anal canal as a whole and this may mean less inter- and intra- observer variability when compared to WPM, as WPM values may vary significantly given this technology only records the maximum pressure value for each variable. Consequently, the Anopress may offer better correlation with reported symptoms than WPM, given it evaluates the sphincter as a whole.

In comparison, WPM provides only maximal resting and squeeze pressures generated by the isolated area of a few mm in the anal canal. This may disregard the contribution of the rest of the muscle complex and it could explain why there has been a poor correlation between manometry and symptoms reported by patients with faecal incontinence. On the other hand, the WPM allows vector volumes measurements. Although this cannot be performed with the Anopress, the clinical value of vector-derived values remains controversial and its clinical relevance is not proved yet (154,155). Also their values are large and difficult to understand (156). The main clinical utility of this measurements in the treatment selection and preoperative

assessment of patients awaiting surgery for anorectal pathology that has yet to be evaluated (156,157).

Finally, the Anopress was better tolerated by patients, who reported lower scores for pain and discomfort. Perhaps this is due to the different designs of the two catheters and from the different position of the catheters during the test: WPM has catheters placed in the anorectum, Anopress catheters are positioned in the anal canal only.

The Anopress catheters were found to have limitations. These included the inability to measure the length of the anal canal and to measure rectal capacity. However, there is some debate in the published literature whether the length of the anal canal is clinically relevant, and its measurement during manometry is unnecessary especially if endoanal ultrasonography is used as correlated test (69). Rectal capacity balloon tests were not possible using the Anopress catheters during the study. This limitation has been addressed by the latest iteration of these catheters that now have a balloon at the tip but they were not available for clinical use at the time of this study. Additional limitations include the fact that this study only assessed two specific products, whereas numerous catheters, technologies and software are available commercially. However, many of the advantages and disadvantages of both the assessed technologies are known to be common issues for all currently available technologies. Another limitation of this study was the lack of a sample size calculation. This could not be performed because the published data on Anopress is scarce and were not sufficient to perform this calculation. Furthermore, the sample size was limited to 60 patients by the medical ethical committee before this study started. The specified sample of 30 men and 30 women could

introduce an obvious selection bias which may have been offset to some degree by the fact that the order patients underwent WPM or Anopress assessment was randomized.

3.5 Conclusion

Normal range values for Anopress have been reported for the first time in this chapter. Anopress device appears able to detect anal sphincter dysfunction in those with symptomatic FI. Most importantly, Anopress measurements correlate strongly with WPM. Anopress also appears to be better tolerated than, and to overcome some of the limitations of, WPM.

4 Evaluation of novel non-invasive treatments

4.1 Introduction

Both conservative and surgical treatments for FI are available but most surgical treatments do not withstand the test of time. Conservative management should be offered first (8,9,141). This ranges from dietary modification and anti-diarrhoeal medication to bowel re-training and biofeedback. Management can be tailored to reflect the individual patient's health, general morbidity, severity and type of FI.

The Renew® Anal Insert (Renew Medical Inc., Menlo Park, California, US) is a recently developed non-invasive therapy for FI (158). It is a single-use anal device (Figure 4.1) that is to be used continuously, with the aim of managing symptoms of passive and or mixed FI. The device can be inserted by the patient with a fingertip applicator. It is made from soft, supple silicone that adapts to patient's anal contours. It is available in two sizes, regular and large. The regular size has a length of 28 mm with an internal cuff of 25 mm, whilst the larger size have length and internal cuff of about 30 mm. Patients are normally advised to start on regular size and if this falls out too easily then they should try the larger size.

The older anal plug devices have failed to gain popularity due to poor patient acceptability, despite an improvement in symptoms in those who persisted with their device (159,160). The hypothesis for this study is that Renew, which is much more malleable compared to other anal plugs, may be more readily acceptable and better tolerated by patients and therefore prove to be an effective treatment for faecal leakage.

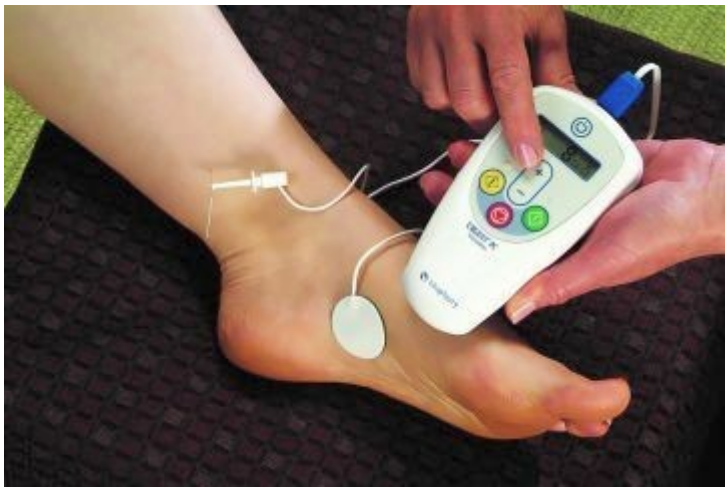
Percutaneous Tibial Nerve Stimulation (PTNS) (Fig. 4.2) is a form of neuromodulation which offers a minimally invasive outpatient treatment. Previous non randomized studies reported good results (91,161,162); however, doubts about the efficacy of PTNS have been raised. A randomized controlled study by Knowles *et al* has suggested that its effect is no better than placebo (94). Furthermore, PTNS is labour intensive and requires regular attendance at a hospital (163).

Both the Renew device and PTNS may be offered to those with therapy refractory FI prior to more invasive treatments such as sacral nerve stimulation, sphincter bulking agents and artificial sphincters. PTNS has been offered to patients with refractory FI for several years (91,162). However, given the concerns about its effectiveness (94), an alternative treatment may be more desirable. The Renew device has had encouraging initial results (164) without the drawbacks of PTNS. It is cheap and can be used from home.

The aims of this study were; 1.) to determine the acceptability of the Renew anal insert and its efficacy for those with passive FI; and, 2.) to compare directly the Renew anal insert and PTNS in patients with passive or mixed faecal incontinence.

Figure 4. 1: The Renew® anal insert and its applicator.

Figure 4. 2: The PTNS device. Courtesy by Laborie Medical Technologies.



4.2 Method

4.2.1 Initial experience with Renew Anal Insert

The study was registered with the local Research and Audit Department (Audit Registration No.SUR.St.M.18.001, London North West University Healthcare NHS Trust) as a service evaluation audit. All patients prescribed the Renew® device, between January 2016 and January 2017, for passive faecal incontinence, were identified in the St Mark's Biofeedback database. Patients were offered a trial of Renew when they were deemed suitable by clinicians. A retrospective case note review of the patients who used this insert was undertaken to identify outcomes of interest.

Patient demographics such as age, gender, parity and prior surgery were collected. The St Mark's faecal incontinence score was recorded at baseline and at the first regular clinic follow-up after a period of Renew Anal Insert therapy. Patients were always advised to start with the regular size and if this falls out too easily then they were advised to try the larger size. As this was a new treatment, a number of other variables were collected including the size of the insert preferred by the patient (regular or large), how many Renew inserts were used per day, how many days of the week they were being used and if patients used other products together with this device. Also, a subjective assessment of symptoms, how beneficial the Insert was, and how satisfied patients were with Renew were all recorded to understand the efficacy and acceptability of the product. Satisfaction was retrospectively assessed from information in the medical records. Subjective reports such as "patient was extremely satisfied" or "patient did not like this treatment" recorded identified in patient medical records were abstracted.

Subjective assessments of patient preference were identified for all patients as this is a new treatment for FI. Major events and side effects were also noted in all cases.

Raw data were expressed as median and range. Statistical analyses were performed using a Wilcoxon Sign Rank test on SPSS (2018, v24, IBM, USA). All data of patients who received Renew during the study period were analysed as per intention to treat approach.

4.2.2 Renew VS PTNS: a randomized blinded pilot study

This investigator-blinded randomized controlled trial of the Renew anal insert versus PTNS in patients with faecal incontinence had received an institutional review board approval by the Health Research Authority (London – Harrow Research Ethics Committee, REC reference 16/LO/1821) prior to initiation. Since there is a paucity of objective prospective studies assessing the effect of the Renew device and PTNS in patients with faecal incontinence no realistic sample size calculation could be performed. Consequently, the sample size was limited to 50 patients by the medical ethical committee before this study started.

4.2.2.1 Patients

Eligible were adult patients with passive or mixed faecal incontinence with a minimum of two or more episodes of faecal incontinence per week as assessed by prospectively collected bowel diaries. Patients recruited to the study had failed previous treatment with biofeedback, pelvic floor physiotherapy or other medical management and be able to self- administer the Renew Anal Insert. This new eligible group of patients were approached in outpatient clinic of St Mark's Hospital by one of the investigators, or by telephone or by mail. The inclusion and exclusion criteria are listed in Table 4.1.

Table 4. 1: Inclusion and exclusion criteria of this study.

Inclusion Criteria	***Exclusion Criteria***
Female or male, > 18 year old	Pregnancy
Passive or mixed faecal incontinence	Inability to given informed consent
Minimum two or more episodes of faecal incontinence per week as assessed by prospectively collected bowel diaries	Known allergy to Silicone.
Failed biofeedback, pelvic floor physiotherapy or other medical and conservative management	Patients who are mentally or physically unable to comply with the protocol of the study.
Able to self- administer the Renew Anal Insert	Inflammatory bowel disease, any active rectal inflammation, Per Rectal bleeding, perianal sepsis
Competent and willing to fill in questionnaires and attend clinics throughout the study	Rectal prolapse, third or fourth degree haemorrhoids, anal stricture, anal or recto-vaginal fistula, previous rectal surgery.

4.2.2.2 Randomisation

Patients were randomized to receive either Renew device or PTNS using the sealed envelope method by a clinician not involved in this study. Recruitment was continued until twenty-five patients were allocated to each group. Patients received either PTNS or the Renew device for a period of three months. All participants were free to withdraw at any time from the allocated treatment without giving reasons and without prejudicing further treatment. At the end of the three-month period patients exited the study and were offered further treatment as deemed appropriate by the treating clinician. The principle investigator was blinded to patient allocation until after the study and data analyses had been completed.

4.2.2.3 Renew Anal Insert

The Renew anal insert (Renew Medical Inc., Menlo Park, California, US) was placed by the patient using a fingertip applicator. All patients randomized to use the Renew device were given the regular and large sizes to use for 2 days prior to starting the trial to determine which size they preferred. The number of inserts used was recorded by the patient. Patients had direct access to the investigating team if they had any concerns, or if problems occurred.

4.2.2.4 Percutaneous Tibial Nerve Stimulation

PTNS was given using a NeuroTracTM TENS transcutaneous electrical nerve stimulator (Verity Medical Ltd, Hampshire, UK) via two 50 mm x 50 mm electrode pads. A fine needle was inserted next to the tibial nerve above the ankle (right above the malleolus) on the inside of the leg. A ground pad attached to the arch of the foot and a barely perceptible electric current was delivered. Continuous stimulation at a current level of 0.5 – 9 mA and a frequency of 10 Hz was used. The amplitude was set to produce a sensory stimulus in the ipsilateral foot, at an

intensity tolerable to the patient. The treatment was given in 12 outpatient sessions of 30 minutes each, once a week at the St Mark's Hospital.

4.2.2.5 Data collection

At enrolment in the study baseline data were collected: patient demographics, duration of symptoms, and type of faecal incontinence, previous surgical and obstetric history. Anorectal physiology tests were always performed to objectively measure the degree of incontinence. Clinical parameters of faecal incontinence were measured at baseline and after 3 months of treatment. The primary outcome measure was a ≥ 50% reduction of episodes of faecal incontinence per week as calculated by a prospectively completed two-week bowel diary (26). This was chosen as primary outcome measure as it reflects the patients' perspective rather than a constructed score by a physician (27), it is also the only validated clinically meaningful and useful primary outcome measure available (28). Secondary outcome measures were St Mark's faecal incontinence score (26), International Consultation on Incontinence Questionnaire-Bowel (ICIQ-B) subdivided in bowel pattern, bowel control and quality of life (29), antidiarrheal agent use, completion of treatment, comfort using a ten-point visual analogue scale (VAS) (1 = comfortable, 5 = ambivalence, 10 = uncomfortable) and acceptability using a similar ten-point visual analogue scale (30).

4.2.2.6 Data analysis and statistical considerations

For consistency pre- and post-treatment data for both cohorts were summarised as the median and inter quartile range (IQR); however, the distribution of data varied between study outcome measures. Differences between groups were assessed for statistical significance with the unpaired T-test (Normal distribution) or Mann Whitney U (Not Normal distribution). Changes

in outcome measures over time were analysed using either a paired t-test (Normal distribution) or the Wilcoxon matched-pairs test (Not Normal distribution). The chi-square test was used to calculate differences in antidiarrheal medication use between groups. Statistical significance was defined as p value < 0.05. Statistical tests were performed using SPSS version 24 (International Business Machines Corporation, Armonk New York, USA).

4.3 Results

4.3.1 Initial experience with Renew Anal Insert

Between January 2016 and January 2017, 30 patients (24 female, median age 59.5 years, range 29-85) received Renew as a treatment for their symptoms of passive faecal incontinence. Twenty-one of 24 women were parous and 8 out of 30 patients had a history of anorectal surgery. All received a starter pack, which allowed them to try both sizes (regular and large). All had failed to improve significantly with first-line conservative treatment including biofeedback. The median follow-up was 11 weeks (range 8-14).

The median St Mark's score at baseline was 15 (range: 7 - 18) and at the first clinic follow-up the score had improved to 10 (2 - 18). Statistical analysis demonstrated a significant difference between pre- and post-treatment scores ($p < 0.0001$) (Figure 4.3).

Eleven (37%) patients used the regular size and 19 (63%) used the large size insert. An average of 1.67 (range 1-3) inserts was used per day. Patients used the insert for an average of 3.58 (1-7) days per week. Of the thirty patients, 18 (60%) continued to use a pad or sanitary towel for protection from bowel leakage, while 12 (40%) used only the Renew insert.

When reviewing the reported symptoms, three patients (10%) reported a slight deterioration in symptoms. Seven (23%) reported no difference, and 20 patients (67%) reported an improvement in their symptoms (Figure 4.4 - B).

All but 4 (13%) of patients were still using the insert at the time of the follow up (median 11 weeks [range 8-14]). The 4 patients had experienced mild pain/discomfort and had stopped the treatment after a few days of discomfort. One patient in this group also reported fresh rectal bleeding. The details of use of Renew by each patient is presented in Table 4.2 by the number of days used per week and the number of inserted per day.

In terms of satisfaction, six patients (20%) said they did not like the Renew insert, while 24 (80%) did like it (Figure 4.4 - A). Four patients (13%) stated that Renew did not work as expected. When considering all 30 patients, 11 (37%) stated that Renew tended to fall out easily, even using the larger size. Three patients (10%) found the insertion difficult. Data are summarised in Table 4.2. Seventeen patients (56.6%) were happy to continue the treatment in the long term. When the St Mark's incontinence scores were compared with patient reported satisfaction there appeared to be a positive association between these variables: patients reported an improvement in symptoms and satisfaction with the device when there was also a significant drop in the incontinence score.

Table 4. 2: Patients using Renew Anal Insert. R = Regular; L = Large; P = Pain/Discomfort; B = Bleeding; F = Fall easily; < = Decreased. > = Increased; SMIS = St Mark's faecal incontinence score.

Patient	SMIS baseline	SMIS follow up	Days per week	Use per day	Additional pads	Size	Adverse event	Leakage episodes	Patient's satisfaction
1	17	9	7	1	Yes	L	F	<	Yes
2	15	10	7	3	No	L	F	<	Yes
3	17	15	4	3	No	L	F	Same	Yes
4	11	12	3	1	Yes	L	P,B	>	No
5	15	11	4	1	Yes	L	0	Same	Yes
6	17	11	1	1	No	L	0	<	Yes
7	17	5	1	1	No	L	F	<	Yes
8	18	10	4	1	No	R	F	<	Yes
9	18	5	3	3	No	L	F	<	Yes
10	17	17	1	3	Yes	L	F	<	No
11	15	15	5	2	Yes	R	0	Same	Yes
12	18	17	4	1	No	L	P	>	No

13	17	10	5	3	Yes	R	P	<	Yes
14	8	2	5	1	No	R	0	<	Yes
15	18	10	5	3	Yes	L	F	<	Yes
16	13	13	1	2	No	R	0	Same	Yes
17	15	11	7	2	No	L	0	<	Yes
18	15	15	3	1	Yes	L	P	Same	No
19	7	2	2	1	No	R	0	<	Yes
20	13	5	3	1	No	R	0	<	Yes
21	11	2	5	1	No	L	0	<	Yes
22	15	10	2	1	No	L	0	<	Yes
23	18	11	3	2	Yes	L	F	<	Yes
24	18	18	4	2	Yes	L	F	Same	No
25	11	7	3	3	No	R	0	<	Yes
26	18	10	1	1	Yes	L	0	<	Yes
27	11	5	3	1	No	R	0	<	Yes
28	15	8	3	1	No	R	0	<	Yes
29	18	7	2	1	No	L	0	<	Yes
30	15	13	3	2	Yes	R	F	Same	No

Figure 4. 3: St Mark's score at the baseline and at the first clinic follow up. The difference was statistically significant ($p < 0.0001$).

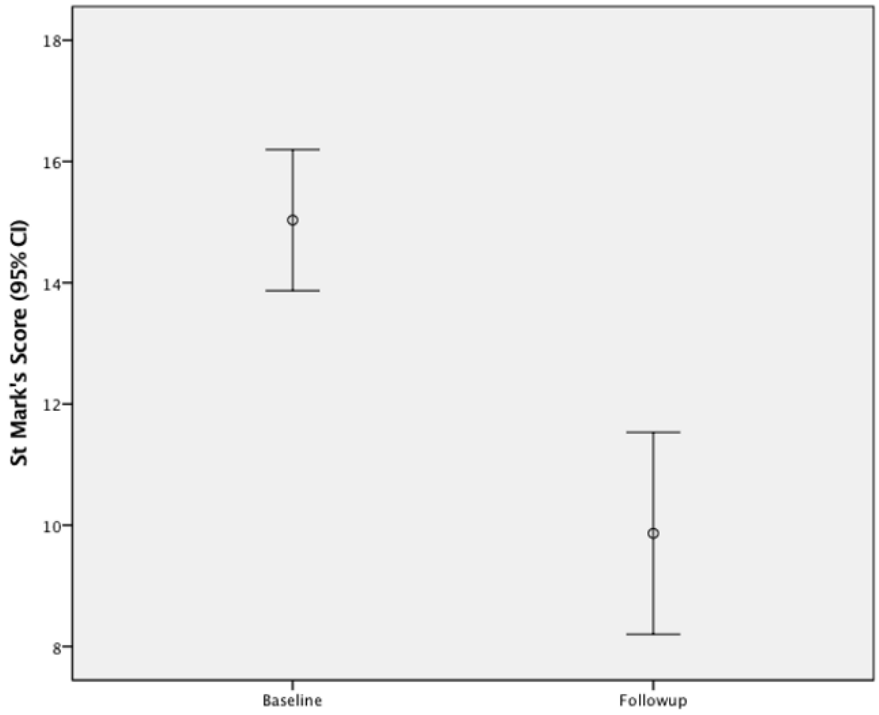
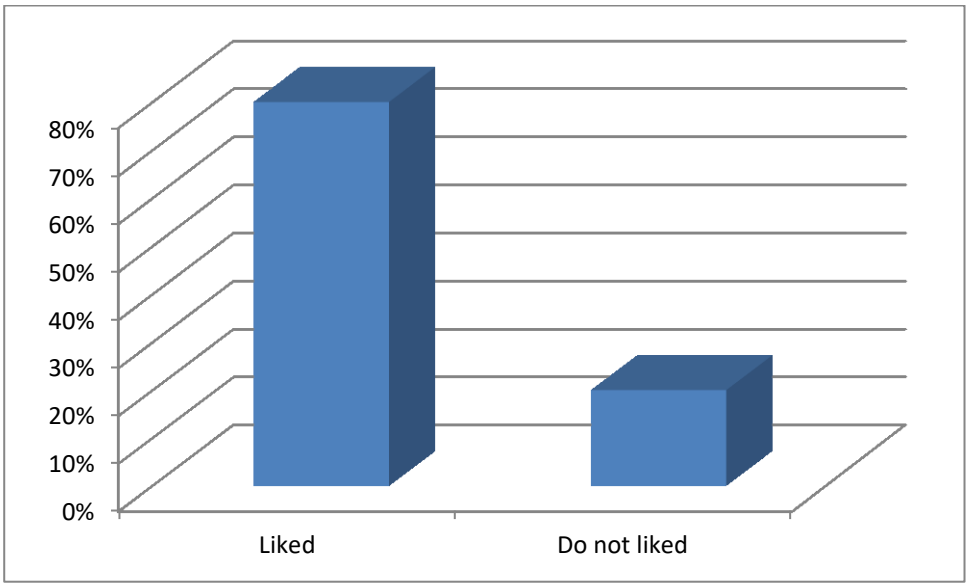
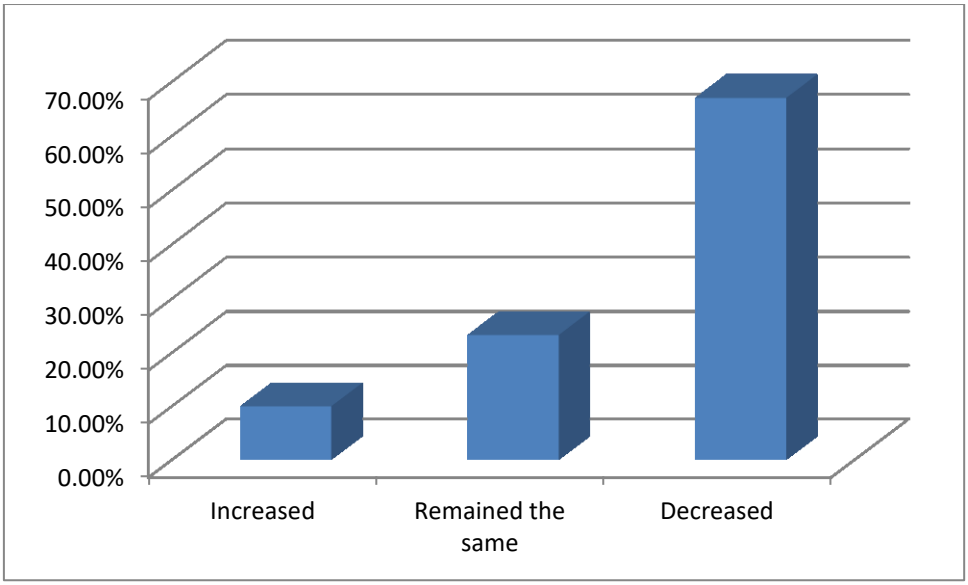


Figure 4. 4: a.) Patient satisfaction with the device and **b.)** Summary of incontinence episodes after Renew treatment.

a.)



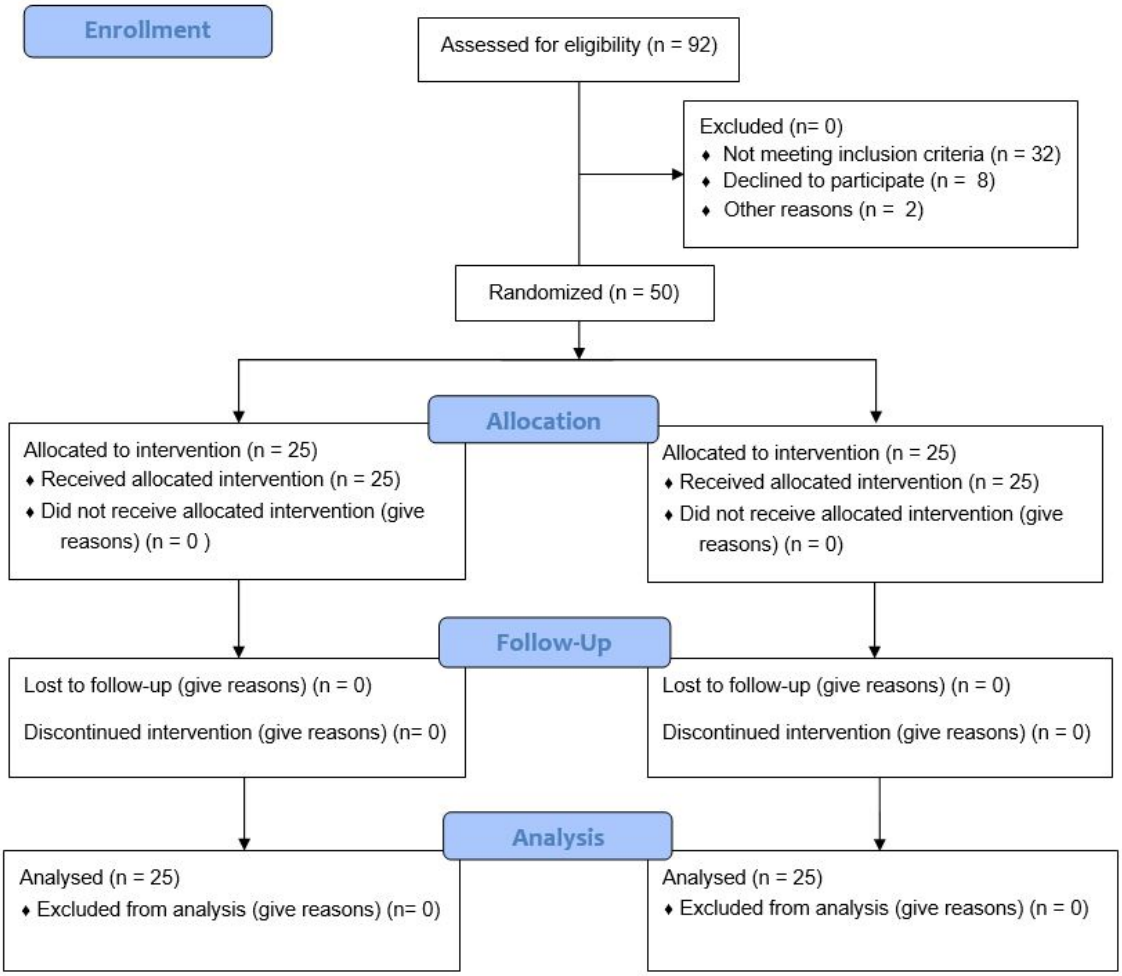
b.)



4.3.2 Renew VS PTNS: a randomized blinded pilot study

A total of 50 patients were recruited to this study between March 2017 and September 2018. During the study period no adverse events were reported. A Consolidated Standards of Reporting Trials diagram of the progress through the phases (enrolment, intervention allocation, follow-up, and data analysis) of a two parallel group is shown in Fig. 4.5.

Figure 4. 5: Consolidated Standards of Reporting Trials diagram of the progress through the phases (enrolment, intervention allocation, follow-up, and data analysis) of a two parallel group randomized controlled trial in adult patients with passive or mixed faecal incontinence that compared the anal inserts group to the weekly percutaneous tibial nerve stimulation group.



4.3.2.1 Baseline data

The median age was 61 years (IQR 47 to 67) in the PTNS group and 58 years in the Renew group (IQR 48 to 63, $p = 0.593$). At baseline there was no statistical difference between the two groups when comparing manometry results (resting pressure $p = 0.272$, maximum voluntary squeeze increment pressure $p = 0.740$, endurance in 5 seconds $p = 0.304$, involuntary squeeze pressure $p = 0.121$). Also there was no difference between the distribution of pure passive and mixed faecal incontinence patients (Renew: Passive FI = 10 patients, Mixed FI = 15 patients; PTNS: Passive FI = 8, Mixed FI = 17). At baseline there was also no statistical difference between the groups when comparing frequency of faecal incontinence recorded by the two-week pre-treatment bowel diary (Renew: median of 18 [IQR 11 to 19]; PTNS 15 [IQR 14 to 18]; $p = 0.716$). Marginally lower but statistically significant St Mark's incontinence (18 [14 - 20] vs. 20 [IQR 18 – 20]; $p = 0.027$) and ICIQ-bowel pattern scores (11 [10-12] vs. 12 [11-15]; $p = 0.042$) were noted at baseline for the Renew group when compared to the PTNS group. No statistical differences were found between the baseline scores of ICIQ-B bowel control ($p = 0.131$), ICIQ-B quality of life ($p = 0.865$) or the use of antidiarrheal medication ($p = 0.128$). All baseline data are shown in Table 4.3.

Table 4. 3: Characteristics of study subjects at baseline. PTNS = percutaneous tibial nerve stimulation. ICIQ-B = international consultation on incontinence questionnaire – bowel. N = Normal distribution of data; NG= Not Normal distribution of data. Statistical significance tested with: a.) Chi square test; b.) Paired T-test; and, c.) Mann Whitney U test.

Baseline	Data distribution	Category	Renew	PTNS	*p*
Gender	NG	Male/Female	2/23	3/22	0.999[a]
Age in years	N	Mean	56 (SD ± 11)	58 (SD ± 15)	0.593[b]
Type of incontinence - **Passive** - **Mixed**		 N 18 N 32	 10/25 15/25	 8/25 17/25	
Duration of symptoms in months		Median 37 months	Median 31 months	Median 38 months	
Obstetric injury		Yes/no	18/7	21/4	0.306[a]
Bowel diary	NG	Median	18 (IQR 11-19)	15 (IQR 14-18)	0.716[c]
St Mark's incontinence score	N	Median	18 (IQR 14-20)	20 (IQR 18-20)	0.027[b]

Baseline	Data distribution	Category	Renew	PTNS	*p*
ICIQ-B bowel pattern (/21)	N	Median	11 (IQR 10-12)	12 (IQR 11-15)	0.042[b]
ICIQ-B bowel control (/28)	N	Median	20 (IQR 16-21)	22 (IQR 18-24)	0.131[b]
ICIQ-B quality of life (/26)	NG	Median	22 (IQR 19-26)	23 (IQR 18-24)	0.865[c]
Antidiarrheal medication	NG	N	14/25	20/25	0.128[c]

4.3.2.2 Results after 3 months

All patients completed treatment; there were no withdrawals or cross overs within the study period. In the Renew group 13 patients used the regular sized inserts, 12 used the large sized inserts. In this group a median of 5 inserts were used per week (IQR range 3 - 6), with a median of 2 (1 to 2) inserts per day.

In the Renew group 100% (n = 25) reported a reduction in episodes of faecal incontinence as recorded by the post treatment two-week diary, versus 88% in the PTNS group (n = 22/25; [p = 0.074]). A ≥ 50% reduction of episodes of faecal incontinence recorded by the two-week post-treatment diary was achieved in 75% of the Renew anal insert group (n = 19/25) and 48% (n = 12/25) of the PTNS group (p = 0.041). After three months of treatment the median number of episodes of faecal incontinence in the post treatment two-week diary was not statistically different between the two groups (Renew: 6 episodes / two weeks [IQR 5 to 8]; PTNS: 8 episodes / two weeks [6 to 9]; p = 0.086).

Both groups showed a significant improvement of the St Mark's FI score and the ICIQ-B scores for FI after 3 months of treatment. The Renew group had significantly better St Mark's FI (Renew: median 11 [IQR 9 - 13] p = 0.001; PTNS: 12 [12 to 15]; p = 0.001), ICIQ-B bowel pattern (Renew: 6 [5 to 10] p = 0.001; PTNS: 8 [8 to 12]; p = 0.002), ICIQ-B bowel control (Renew: 11 [9 to 16] p = 0.001; PTNS 17 [11 to 20]; p = 0.001) and ICIQ-B quality of life (Renew: 15 [12 to 16] p = 0.001; PTNS 16 [14 to 20]; p = 0.001) scores when compared to PTNS. Fewer people used antidiarrheal medication after 3 months in the Renew group, (Renew: Y/N 10/15 p = 0.827; PTNS 16/9 p = 0.016). These results are reported in Table 4.4 and depicted in Figure 4.6.

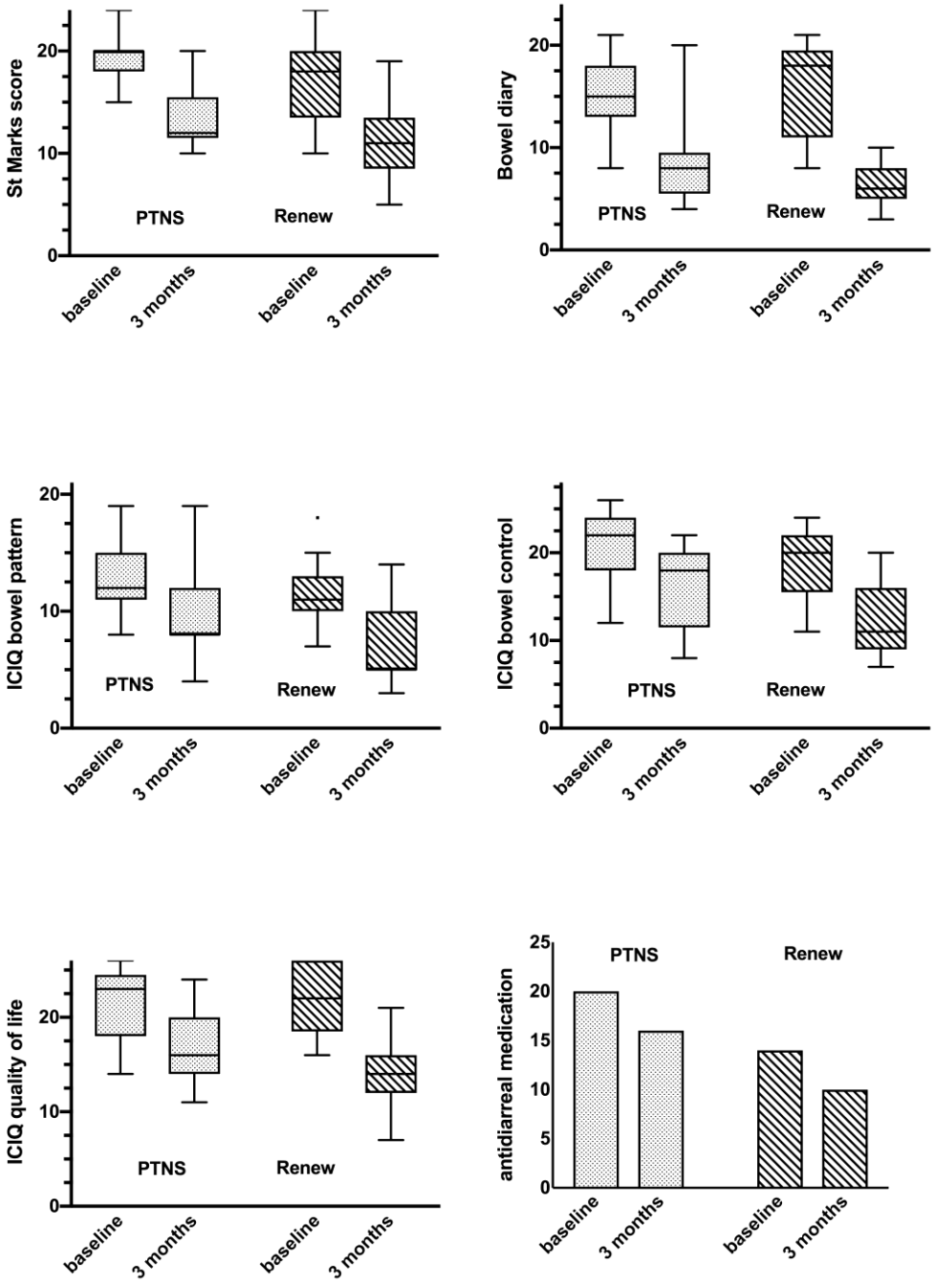
Some patients reported some degree of discomfort using the Renew insert. When assessed using a visual analogue scale for discomfort, 8 patients did not report any discomfort, 15 patients reported a score of between 1 and 3, while 2 patients reported a score of 4. When assessing acceptability using a visual analogue score, 17 patients reported it was entirely comfortable; eight patients reported scores of between 1 and 3 indicating some degree of minor discomfort but no patients reported major pain or distress. None of the patients in the PTNS group reported any discomfort of treatment, with all patients reporting zero for both discomfort and acceptability.

Table 4. 4: Comparison within the groups between clinical parameters of faecal incontinence at baseline and after 3 months of treatment. PTNS = percutaneous tibial nerve stimulation. ICIQ-B = international consultation on incontinence questionnaire – bowel. G = Normal distribution of data; NG = Not Normal distribution of data. Statistical significance tested with: a) Paired T-test; b) Mann Whitney U test; and, c) Mc Nemar.

Renew anal insert	**Data distribution**		**Baseline**	**3 months**	***p* value**
FI in a 2-week bowel diary **Any improvement** **≥ 50% improvement**	NG	Median %(N) %(N)	18 (IQR 11-19)	6 (IQR 5-8) 100 (25/25) 75 (19/25)	<0.001[a]
St Mark's incontinence score	N	Median	18 (IQR 14-20)	11 (IQR 9-13)	<0.00 [b]
ICIQ-B bowel pattern (/21)	N	Median	11 (IQR 10-12)	6 (IQR 5-10)	<0.001[b]
ICIQ-B bowel control (/28)	N	Median	20 (IQR 16-21)	11 (IQR 9-16)	<0.001[b]
ICIQ-B quality of life (/26)	NG	Median	22 (IQR 19-26)	15 (IQR 12-16)	<0.001[a]
Antidiarrheal medication	NG	Y/N	14/11 (56%)	10/15 (40%)	0.827[c]

PTNS	**Data distribution**		**Baseline**	**3 months**	***p* value**
FI in a 2-week bowel diary - **Any improvement** - **≥ 50% improvement**	NG	Median %(N) %(N)	15 (IQR 14-18)	8 (IQR 6-9) 88 (22/25) 48 (12/25)	<0.001[b]
St Mark's incontinence score	NG	Median	20 (IQR 18-20)	12 (IQR 12-15)	<0.001[b]
ICIQ-B bowel pattern (/21)	N	Median	12 (IQR 11-15)	8 (IQR 8-12)	0.002[a]
ICIQ-B bowel control (/28)	NG	Median	22 (IQR 18-24)	17 (IQR 11-20)	0.001[b]
ICIQ-B quality of life (/26)	N	Median	23 (IQR 18-24)	16 (IQR 14-20)	<0.001[a]
Antidiarrheal medication	NG	N	20/5 (80%)	16/9 (64%)	0.345[c]

Figure 4. 6: In graphs a, b, c, d, e scores are represented in Tukey box-and-whisker plots: the boxes represent quartiles, the band inside the box represent the median. The whiskers represent the total range of data. In the bar chart labelled f the number of patients that are using antidiarrheal medication is indicated.



4.4 Discussion

For patients with passive faecal incontinence a significant improvement in St Mark's Incontinence Score was seen with the Renew Anal Insert at 12 week follow-up. The first study reported in this chapter demonstrated that 80% of patients reported they liked this device. This study also identified that 67% of patients experienced a subjective improvement in symptoms, correlating with the objective reduction in incontinence scores reported in this chapter. This study also demonstrates that the Renew device is an effective conservative treatment for passive FI. However, only 56% of patients included in this study were prepared to continue with the device in the longer term.

Comparing results of this evaluation to the other published work assessing this device results were similar but not identical. Lukacz *et al*, in a study funded by Renew Medical Inc., reported the outcome measures of 91 patients with all types of FI, who were offered the renew device for a 12-week treatment period. Seventy-three completed the 12-week treatment period (80%) (164). On an intention-to-treat basis, 62% of patients achieved a >50% reduction in the frequency of FI episodes. The mean frequency of FI episodes per day was reduced from 1.1 +/-0.9 to 0.3+/-0.4 (p<0.001) at the end of 12 weeks. Fifty-seven patients (62% on intention-to-treat analysis) were extremely satisfied with the device (164). It is important to note that Lukacz *et al* included those with faecal urgency in their study too. Consequently, the presumption that anal inserts are suitable only for those with passive soiling may be incorrect. This deserves further investigation.

The results of Lukacz *et al* agree with previous work from our group (165). This was a small prospective study from our centre that demonstrated improved symptoms when using the

Renew insert for 15 patients who had undergone restorative proctocolectomy with ileal pouch anastomosis and were experiencing FI. In this specific group the Renew device was acceptable to 53% (8/15) and was effective in 40% (6/15) of patients (165).

The Renew device appears to be well tolerated. Only four patients reported it to be uncomfortable, one of whom reported some minor rectal bleeding. This device is reported to be soft, comfortable and seals off the rectum from the inside. Consequently, this device may have overcome some of the disadvantages of the more established Peristeen anal plug (85) which, in a recently published systematic review, seems to have poor patient acceptability, an offensive smell, faecal leakage, local irritation and contributes to a sensation of urgency (64). The Renew device was not easily retained in 11 patients. This may reflect the fact that this was used solely in those with passive FI. Very often, these patients will have a low resting pressure with a deformed anal canal that may not even close at rest. These factors make retention of any anal device difficult. The Eclipse System is another similar treatment (165). However, this is a vaginal insert and currently does not have a CE mark for use in the European Union. To our knowledge there are no other similar treatments available in the UK market.

This study has several limitations. It was a retrospective single institution series. The group of patients was small, follow-up was short, and the population was limited to patients treated at one institution. Bowel diaries were not used for all patients or, as often happens, incorrectly filled in; therefore, the patient's reported recollection of improvement in incontinence episodes may have recall bias. The presented data are limited to those who actually used the device; those for whom it was recommended but was not used are not included in this study. However, the pragmatic nature of this study perhaps reflects "real life" clinical practice.

This single blinded randomized controlled pilot study showed a significant reduction in symptoms of FI after 3 months of treatment with both the Renew anal insert and PTNS. The Renew anal insert proved to be slightly more effective. Seventy five percent of those who received the Renew device achieved a ≥ 50% reduction in episodes of faecal incontinence as reported in the two-week diary compared to 48% in the PTNS group. The St Mark's and the ICIQ-B faecal incontinence scores reported by this study also seem to favour the Renew anal insert. These results suggest that this relatively new treatment is an attractive alternative to PTNS in patients with faecal incontinence that have failed conservative treatment, and the presented data will prove helpful when counselling patients who are about to start this therapy.

Another advantage of the Renew anal insert over PTNS is that the patient can apply the insert at home and does not have to attend hospital on a weekly basis. This could save time and cost for both the patient and the National Health Service. The Renew anal insert in the UK costs £2.60 per insert and is available on prescription from the UK National Health Service. Conversely, the cost for a full PTNS treatment (12 sessions) is £456.83. This does not take into account the cost of the reusable machine (£990.77) and the cost of running the clinic including staff salaries. This arrangement may differ in other countries. It will be important in future to investigate the cost of the Renew insert and PTNS further in a separate formal cost analysis.

To our knowledge this is the first study which has directly compared the Renew device to PTNS. The strengths of this study include the prospective randomized design and the double-blind fashion in which the investigator analysed the results. This study also has some

limitations. Firstly, a relatively small sample of patients were recruited. Given the paucity of objective prospective studies assessing the effect of the Renew device and PTNS for patients with faecal incontinence no realistic sample size calculation could be performed, and the sample study size was limited to 50 patients by the medical ethical committee prior to commencement of the trial. Secondly, it could be argued that PTNS and Renew anal insert have different mechanisms of action and thus do not have to be compared in a randomized way, given both these treatments are safe and efficacious for some FI cohorts and are therefore can be safely trialled for patients who have failed conservative treatment measures. However, the hospital and patient costs associated with PTNS therapy are significantly greater in the shorter term. As the Renew anal insert proved to be slightly more effective in this study it would seem to be the preferred first line treatment for patients who have failed conservative treatment measures described previously. Conversely, if the Renew insert is used in the long term the cost of using several inserts per day may ultimately prove more expensive than PTNS therapy including any additional therapeutic sessions that are required. It is important to highlight only short-term follow-up data are presented by this study for the Renew insert and the long-term efficacy remains unknown. While the long-term results from PTNS have already been widely demonstrated (90,95,138,161,162,166) it is not clear if patients will continue to use the Renew insert on an ongoing basis every day, which may limit the utility of this device.

4.5 Conclusion

The Renew device appears to be a safe, well tolerated and effective treatment for passive FI. The randomized pilot study suggests that both the Renew device and PTNS are effective treatments for FI. It also suggests that the Renew device may be more effective than PTNS but

only half of the study population would be willing to use this in the longer term. Larger studies will be required to investigate the long-term efficacy of the Renew insert.

5 Evaluation of invasive treatments

5.1 Introduction

The multifactorial aetiology of faecal incontinence typically guides the choice of management. As discussed in Chapter 1.8.1, conservative management of faecal incontinence includes drug therapy, pelvic floor rehabilitation, biofeedback, inserts and plugs, PTNS. However, the efficacy of these treatments can sometimes be unsatisfactory (8,83)(53). Procedures such as sphincteroplasty, dynamic graciloplasty, and artificial anal sphincter placement can be considered to treat severe faecal incontinence but can cause substantial comorbidity and have variable outcomes (112,122,124,167,168).

The most commonly used and effective form of neuromodulation is Sacral Nerve Stimulation (SNS), nowadays known as Sacral Neuromodulation (SNM) (Fig. 1.14). This is an effective approach for a variety of faecal incontinence conditions, but expensive and a lifelong journey (107,169,170). It was first reported for urinary dysfunction by Tanago in 1988 (171) and for FI by Matzel in 1995 (172). A wide range of published literature supports its use in the short and medium term (173–176). However, only a few reports have investigated its efficacy over a longer term (101,108,177).

An alternative new technique is the injection of bulking agents, which has been used previously as a safe alternative in patients with faecal incontinence due to internal anal sphincter deficiency, although there are no guidelines or robust outcome measures reported for this treatment and long term outcomes remain questionable (111,113,114). Conventionally, the injection of prosthetics in the intersphincteric plane relies on the bulking effect of the

implantable agent, subsequent fibrosis and collagen deposition. In the past, a number materials such as autologous fat, glutaraldehyde cross-linked collaged (Contigen), pyrolytic carbon beads (Durashere), silicone biomaterial (PTQ, Bioplastique), dextranomer (NASHA Dx, Solesta) have been trialled (178–181). Injectable agents have been reported to be more successful than sham treatment in a double blind randomized controlled trial, with a success rate of 50-70% (178). Early reports of a self-expanding device of polyacrylonitrile (Gatekeeper) showed a sustained improvement of faecal incontinence over a follow up period 33 months (113).

The implantation of biomaterials has gained acceptance and has led to the development of newer bulking agents: the SphinKeeper prostheses (THD Sphinkeeper, THD SpA, Correggio [RE], Italy) (118). These are also made from hyexpan (polyacrylonitrile). After implantation the prostheses expand and change their size and physical properties within 48 hours of contact with fluids becoming shorter, thicker and softer over time. They remain identifiable by palpation and ultrasonography within a soft fibrous coat caused by the host reaction. Sphinkeeper differs from the Gatekeeper technique as the injectable agents are bigger and a different number of prostheses are used.

Sphinkeeper also differs from other bulking agents as it does not simply aim to augment the internal anal sphincter, but rather to form an artificial anal sphincter by creating a circumferential mechanical layer located into the intersphincteric plane. Once inserted in this plane it is hypothesized that Sphinkeeper will provide extrinsic compression of the internal anal sphincter and close the anal canal at rest. The presence of these prostheses may also improve the function of the external anal sphincter by helping to transmit the contraction of the

external sphincter and possibly generate a more effective squeeze (182). However, the evidence supporting the clinical use of this technique is still very limited. At the time of writing there are only three small prospective studies that reported preliminary results with this new treatment. All off these studies assessed a small group of patients over a short follow up period (118,182,183).

The aims of this chapter were to: 1.) investigate the long-term (> five year) functional outcome measures associated with SNM for FI, with specific reference to validated FI scores; and, 2.) to review and critically analyse the safety, feasibility and short-term effectiveness of Sphinkeeper again using validated FI scores in a larger UK multicentre cohort of patients.

5.2 Method

5.2.1 Evaluation of the long-term outcome of Sacral Neuromodulation

The data of all patients who had undergone permanent SNM since 1996 were recorded in a prospective collected database. This database was interrogated to identify those who had undergone SNM for FI, which was the only inclusion criterion for this study. Patients undergoing SNM for other reasons were excluded from this study. Patients who had undergone permanent SNM implantation with less than five years of follow-up, or who had incomplete data, were also excluded from this study. The following data were abstracted from the database: date of implantation, date of first and last clinic follow-up, length of follow-up, surgical complications and validated continence scores.

Patients were only considered for SNM when all available conservative treatments for FI had failed. All patients included in this study had a successful trial of peripheral nerve evaluation (PNE) using a unipolar lead (Medtronic, Minneapolis, Minnesota, USA; model 3057) prior to permanent implantation. Patients who had successful PNE were offered permanent SNM implantation (Medtronic; lead models 3889 and/or 3093; IPG models Interstim until 2011 and Interstim II since then). Surgical implantation was performed positioning a quadripolar lead in S3 or S4 in a standardised way following national and international guidelines for SNM (See Section 5.2.1.1 (102,106).

Success of PNE was determined by assessment of prospectively collected patient bowel diaries. A 50% reduction in the number of FI episodes per week or a 50 % reduction of validated FI scores after 3 to 4 weeks of PNE was deemed to be a successful response. While bowel diaries were always used following PNE these results were not uniformly included in our database for the study period and therefore were unavailable for analysis. Functional outcome after both PNE and permanent SNM implantation was evaluated only by the St Mark's FI score (Appendix 2). FI scores were recorded at baseline, at six-month follow-up and at the last available clinical follow-up (medium-term follow up). Also, patients received a telephone follow up at the time of this study (long-term follow up). Data were expressed as median and range. Patients who could be contacted to assess long term follow up were also asked if they perceived they still benefited from SNM and whether they would like further clinical review.

Following permanent SNM implantation, overall long-term success was defined as ≥ 50% reduction of the validated FI scores, as this has remained the standard for primary outcome responder analysis in the most recent major studies (100,134–137). Also, a number of patients

with full continence and number of patients with worsening scores were recorded. Factors associated with SNM outcome measures and the impact of other co-varieties (age, gender, type of incontinence) were analysed by univariate logistic regression.

Statistical analyses were performed using GraphPad (GraphPad Prism Software Version 6, La Jolla, CA, USA). The two-tailed t test was used for paired comparison of continuous data. P-values of < 0.05 were considered statistically significant. All values were expressed in median and range. Analyses of predictors of successful and unsuccessful permanent SNM implantation were performed by binary logistic regression.

In this study I was involved in the collection of data, analysis and interpretation of the results.

5.2.1.1 Standardised operative procedure

Patients whom passed the trial were listed for permanent placement of SNM. The patient were normally positioned in the prone position under general anaesthesia on the operating table. Prophylactic antibiotic was always given. Feet and toes were always lifted off the table to ensure direct visualisation of toe and foot response upon stimulation. The first series of patients underwent an open surgical procedure where the lead was placed after a midline incision inside the third sacral foramen under direct visualization. With the introduction of the percutaneous lead placement, the procedure was performed in a blinded standard way using reliable landmarks. These include the superior iliac spine, the L5-S1 transition, the tip of the coccyx or tip of the sacrum, the sciatic notch, and the midline. Based upon these landmarks, the presumed bony location of S3 foramen could therefore be drawn on the skin, marking the needle entry

point. This positioning was always carried by the help of intra operative x-ray. The procedure continued with the insertion of the needle into the third sacral foramen, and once at this indicative level, testing stimulation could be performed with the external pulse generator. Normally the aim was to achieve an anal motor response (bellows) and a toe/forefoot response at a lowest current impulse (< 2mA). Then the needle stylet was removed and the directional guide inserted. A small skin incision was performed to facilitate the positioning of the introducer. The next step was to remove the needle leaving the guidewire in place. Finally the SNM lead was inserted under fluoroscopy. A small incision (about 5 cm) was performed in the ipsilateral buttock, a small subcutaneous pocket created and the lead tunnelled to the pocket. The final step was to connect the lead to the SNM generator (IPG). Wound was always closed with absorbable stiches.

5.2.2 Sphinkeeper: first multicentre experience in the UK

5.2.2.1 Data collection

Data on the first cohorts of patients treated for faecal incontinence with SphinKeeper in two major tertiary referral centres in the UK were prospectively collected using a specifically designed registry and retrospectively analysed. The two registry differ between the two centres as there was no initial intention to prospectively evaluate the two services together. Hospitals were: The Royal London and Whipps Cross Hospitals (part of Bart's Health NHS Trust: hereafter 'BARTS') and St Mark's Hospital (SMH) (part of London North West University Healthcare NHS Trust). In this study I was involved in the construction of the registry, surgery, collection and analysis of the data for BARTS and only on collection and analysis of data for

SMH. This service evaluation was registered with the local research and audit departments (London North West NHS Trust Research & Development Office, SUR.StM.20.030; Bart's Health NHS Trust, No 7068A).

5.2.2.2 Standardised preoperative care

As part of routine management, anorectal physiology investigations including anorectal manometry and endo-anal ultrasonography (EAUSS) were performed to assess anorectal function and morphology. Colonoscopy was performed only if indicated. At BARTS, manometry was performed using a high-resolution anorectal manometry system (Solar GIHRM v9.1; MMS), utilizing a solid-state catheter incorporating 12 microtransducers (UniTip: UniSensor AG, Attikon, Switzerland). Normal values were based on our previously published work (138). At SMH, manometry was also performed using a high-resolution anorectal manometry system (Solar GIHRM v9.5; MMS), utilizing water-perfused catheters incorporating 10 microtransducers spaced at 8 mm intervals. Normal values were based on previously published work (27,28). Anal hypotonia was defined as resting tone below normal limits; anal hypocontractility was diagnosed if maximum voluntary incremental squeeze pressure was below normal limits (29).

5.2.2.3 Standardised operative procedure

All patients in both centres were prepared with a phosphate enema. Antibiotic prophylaxis was always given intravenously in theatre (generally penicillin). Patients were operated on under general anaesthesia in the lithotomy position. Povidone iodine solution or cetrimide and chlorhexidine gluconate solution were used to disinfect the skin. Ten equally spaced 2-mm

perianal skin incisions were made 2 cm from the anal verge on the anoderm side, avoiding the 12 o'clock position to prevent any possibility of injury to the vagina or urethra. The Sphinkeeper delivery system was loaded before each insertion, by pushing an activating button for 5 seconds resulting in the extrusion of a guiding cannula (Fig. 5.1). Under digital guidance (BARTS) or ultrasonography guidance (SMH), the introducer was then inserted into the intersphincteric space through a short subcutaneous tunnel and pushed up to reach the upper part of the anal canal, corresponding to the puborectalis muscle level (Fig. 5.2). After firing the delivery system allowed the cannula to retract and the prostheses were deployed. The skin wounds were closed with absorbable sutures. Postoperatively, all patients were instructed to minimize mobilisation for a minimum of 48 hours to reduce the risk of early prosthesis dislocation. Lidocaine gel and systemic painkillers were prescribed as needed for postoperative pain. A five days course of oral antibiotics was used. It is highlighted here that the technique used followed previous publications and device manufacturer instructions. The ideal position of prosthesis placement was also based on previous publications (117,118,183).

Figure 5. 1: The Sphinkeeper delivery system. The prosthesis increase in size after delivery in the intersphincteric space.

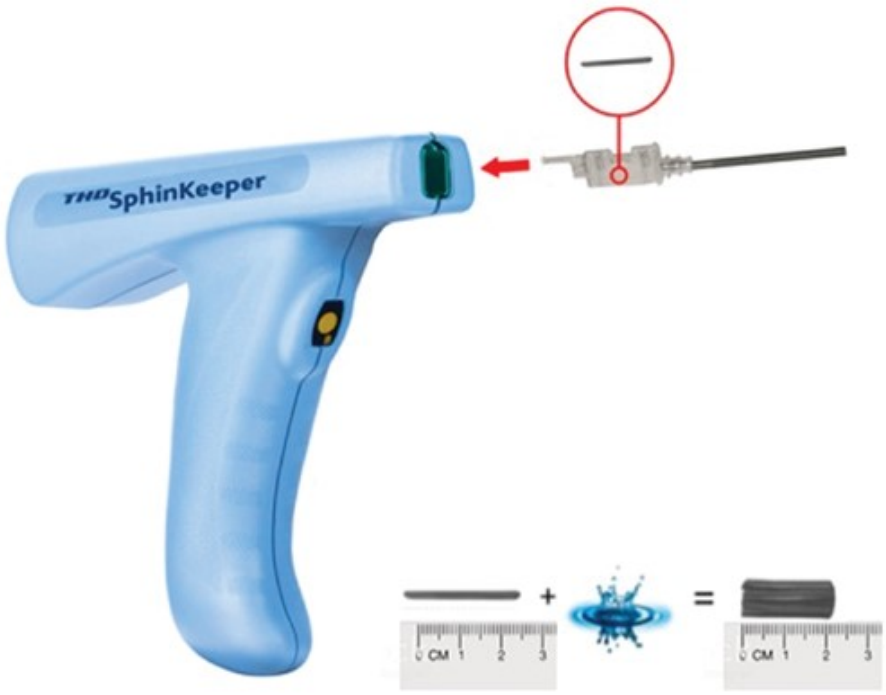
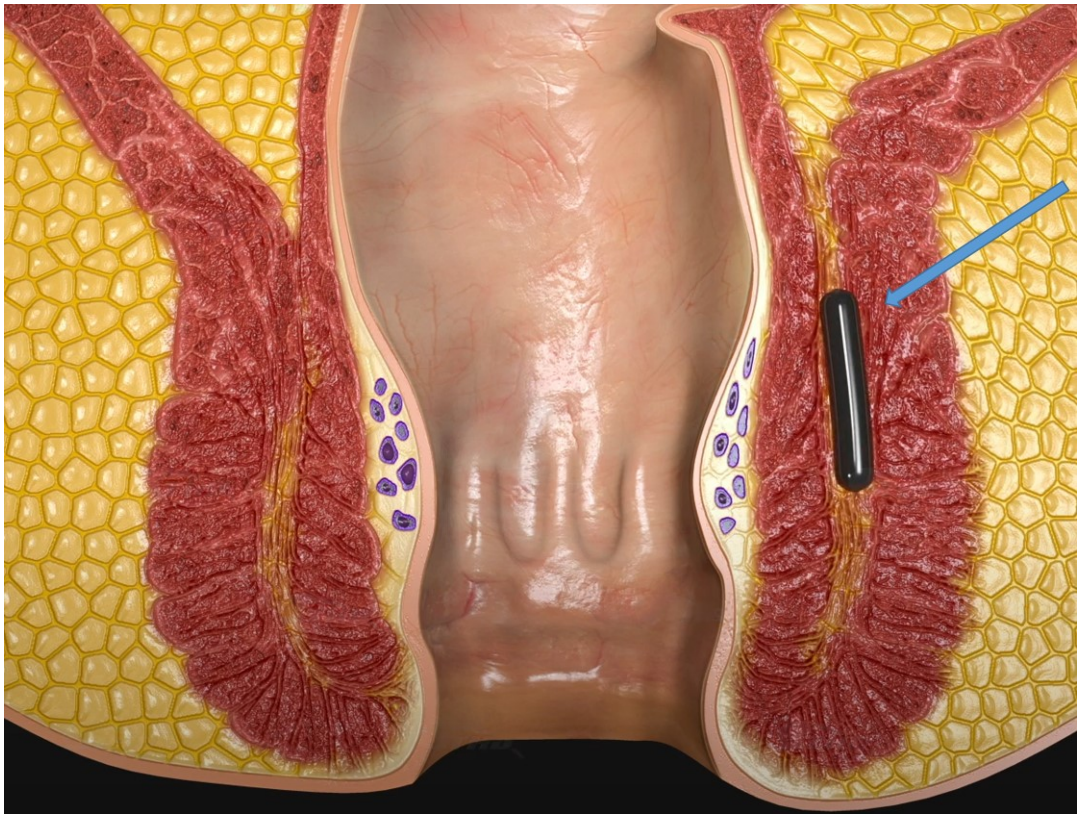


Figure 5. 2: The Sphinkeeper prosthesis are directed and positioned into the intersphincteric space through a short subcutaneous tunnel and pushed up to reach the upper part of the anal canal. The arrow indicates a prosthesis placed in the ideal part of the anal canal. With courtesy of THD SpA.



5.2.2.4 Postoperative results / follow up

Data on intra- / postoperative complications and St Mark's scores were collected by reviewing all operation notes, discharge letters, and hospital visits in the pre and postoperative period. Standard postoperative imaging was used to confirm the positioning of the introduced prostheses for most patients.

5.2.2.5 Review of postoperative imaging

All anonymized EAUSS and MRI were reviewed retrospectively by an expert sonographer or an expert gastrointestinal radiologist. The total number of prostheses and their location on the anal canal was reviewed. EAUSS viewing software (BK3d viewer version 7.0.0.522, by Medical APS, Mileparken 34, 2730 Herlev) was used to assess implants for patients who had not undergone MRI.

5.2.2.6 Statistical analysis

Results have largely been presented descriptively (symptom scores, incidence of adverse events and radiological findings). For efficacy data, 'success' was defined as reduction of ≥ 50% in SMIS after treatment (100,141–144) with before-and-after comparison of incontinence scores analysed using a paired t-test. Other limited comparisons were made statistically to give an indication of effect of centre. The relationship between number of prosthesis and categorical outcome (based on 50% reduction in SMIS) was presented as contingency table and analysed

using Chi Square analysis. Statistical significance was defined as $p < 0.05$. IBM SPSS software (Vers. 2018, IBM PO Box 41, North Harbour, Portsmouth) was used for these analyses.

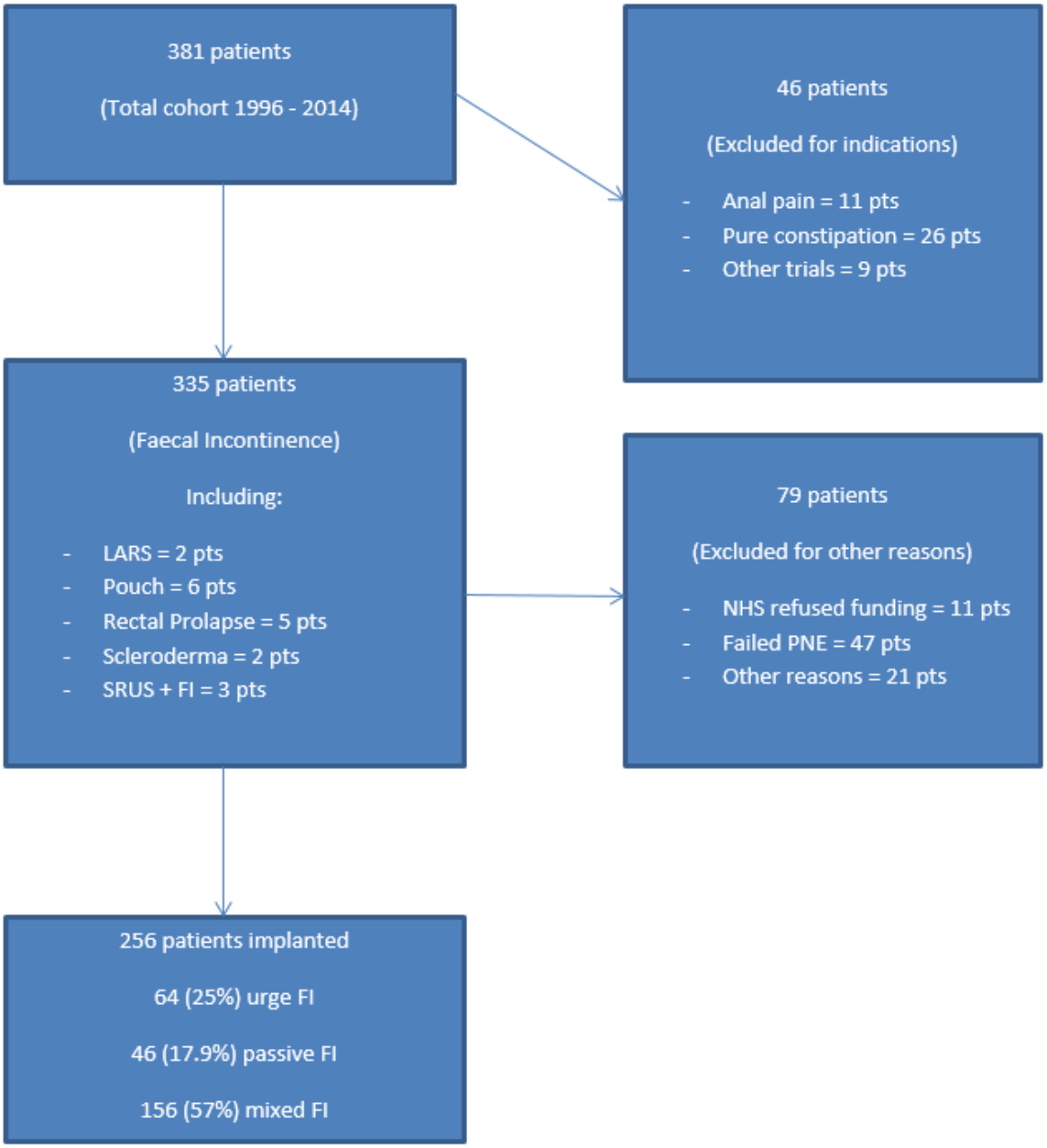
5.3 Results

5.3.1 Evaluation of the long-term outcome of Sacral Neuromodulation

5.3.1.1 Demographics

Between January 1996 and December 2014, a total of 381 patients were initially considered for SNM. For the purpose of this study, 46 patients were excluded from the analysis as they received SNM as a treatment for other reasons, such as anal pain, constipation or as part of other research trials. Of the remaining 335 patients, 47 patients failed PNE and a total 256 patients (205 female – 80%; 51 male – 20%) met the study inclusion criteria (Fig. 5.3). The median age at the date of SNM permanent implantation was 52 years (range 18 - 81). In this cohort 64 (25%) patients had urge, 46 (17.9%) had passive and 146 (57%) patients had mixed FI. Twenty-one patients were lost at the medium-term follow up point of 110 months (12 - 270). The long-term median follow-up period for all patients included in this study was 132 months (60 - 276) after permanent SNM implantation. However, long-term follow-up data were not available for 71 patients (27.7%), 7 of whom had passed away, 11 refused to engage with long-term follow up, and the remaining 53 patients were uncontactable.

Figure 5. 3: Total cohort recorded in the database and number of total patients with SNM included in the analysis. Pts = patients; LARS = Low Anterior Resection syndrome; SRUS = Solitary Rectal Ulcer syndrome.



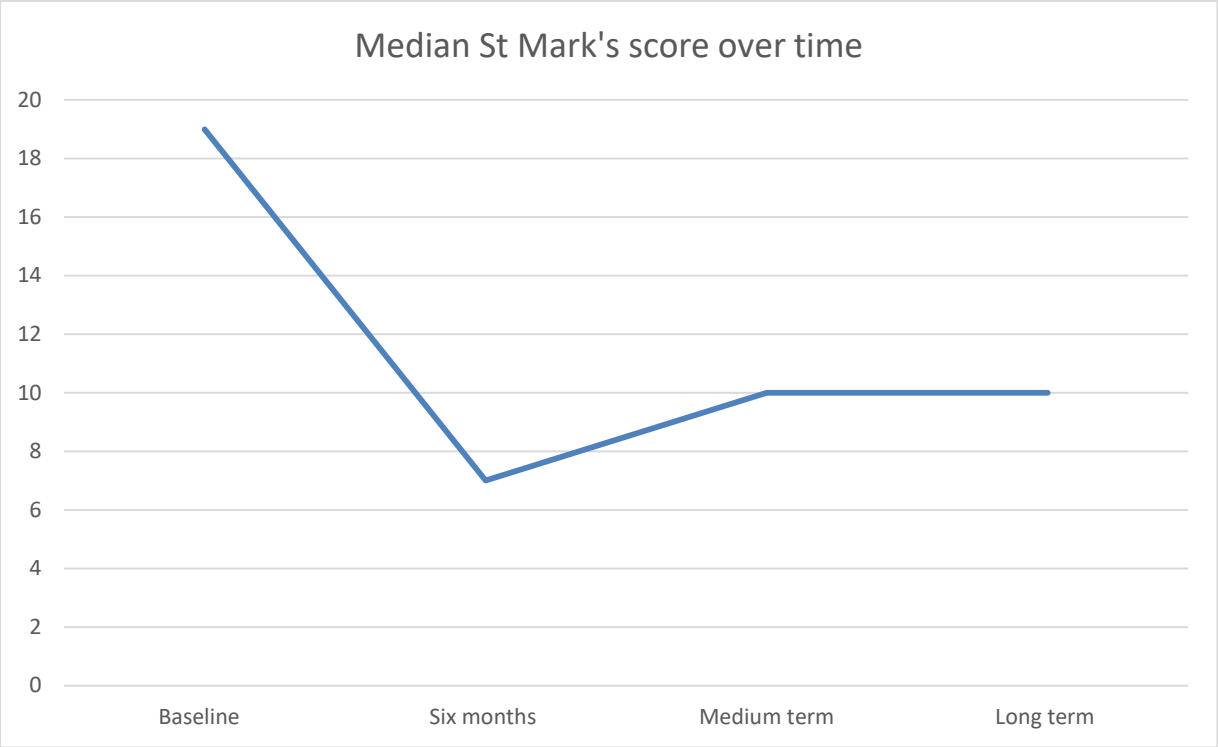
5.3.1.2 Overall results

For the total cohort of 256 patients, the median baseline FI score was 19/24 (9 – 24) while the six month median FI score was 7/24 (0 - 24), representing a significant reduction from baseline ($p < 0.00001$). At medium-term follow up (110 months [range 12 - 270]), the St Mark's score for the 235 patients was 10/24 (0 – 24; $p < 0.00001$) and at the long-term telephone follow up (132 months range [60 - 276]) the St Mark's score was 10/24 (0 – 21; $p < 0.00001$), again representing significant reductions from baseline (Table 5.1 and Fig. 5.4). When FI scores at medium-term follow up (10/24) were compared with long-term follow up FI scores (11/24) there was no statistically significant difference between these time points (NS; $p = 0.92828$).

Table 5. 1: Overall St Mark's FI scores in the study cohort. P values represent the difference between baseline and each follow up point. The two-tailed t test was used for paired comparison of continuous data. P-values of < 0.05 were considered statistically significant.

	Baseline	**First follow-up**	**Medium-term follow up**	**Long-term follow up**	***p* value**
Follow-up	**-**	6 months	Median 110 months (range 12-270)	Median 132 months (range 60-276)	**-**
St Mark's FI score	19/24	7/24	10/24	10/24	$p<0.00001$

Figure 5. 4: Median St Mark's FI scores for all patients at baseline, 6 months follow up, medium-term follow up and long-term follow up.



5.3.1.3 Extent of response

Of the 256 patients, 167 (65.2%) at six months follow up had a reduction of more than 50% in their St Mark's FI scores. The median FI scores for this subgroup when compared to baseline was 5/24 (0 – 14; $p < 0.00001$). Full continence was achieved in 21 patients (12.5%). For the remaining 89 patients (34.7%) that had a reduction of less than 50% in their St Mark's FI scores the median FI score was of 13/24 (7 – 24; $p < 0.00001$) when compared to baseline. Five patients (5.6%) reported no change in continence scores, while 3 (3.3%) patients reporting an increase in their FI scores.

At medium-term follow up, the number of patients with a 50% or greater improvement in FI score dropped to 142 (60.4% of the total cohort), although the median FI score had stabilised at 5/24 (0 – 15; $p < 0.00001$) when compared to the baseline. Of this group, 27 patients (11.4%) reported full continence. Of the remaining 93 patients (39.5%) the median FI score was of 13/24 (7 – 24; $p = 0.00038$) when compared to the baseline. The number of patients with no change in continence scores was 4 (10.2%); 17 patients (43.5%) reported an increase in their incontinence scores.

Of the 185 patients available at long-term follow up, 115 (62.1%) had a ≥ 50% improvement in FI score with a median of St Mark's score of 5/24 (0 – 11; $p < 0.00001$) when compared to baseline. All 115 patients reported that they had a good and sustained response from SNS and would not wish to interrupt the therapy. Of that cohort, 12 patients (10.4%) reported full continence. Of the remnant 70 patients (37.8%) the median FI score was of 13/24 (7 – 21; $p = 0.002$) when compared to the baseline. Of this subgroup, 13 (18.5%) patients reported no change or a deterioration in incontinence score and 12 (17.1%) reported in increase in their

incontinence scores. Thirty-six of the 185 patients interviewed were unwilling to undergo further investigations or clinical assessment for a variety of reasons (age, comorbidities, and other priorities). Outcome measures over time are summarised in the Table 5.2, 5.3 and 5.4.

Passive faecal incontinence had a significant association with the likelihood of successful permanent SNM outcome at 6 month follow up, however this did not show any impact in the medium and long term. There was no significant association between age, gender and other type of incontinence and the likelihood of successful permanent SNM outcome on regression analyses. Baseline St Mark's score was the only value to have significant association with the likelihood of successful permanent SNM outcome in short, medium and long term. Factors associated with functional outcome are reported in Table 5.5.

Table 5. 2: Extent of response in the 256 patients who underwent 6 months, medium and long -term follow up. *Note that 21 patients were lost at the medium-term follow up and at long-term follow-up the results were not available for 71 patients. Success was defined as ≥ 50% reduction of the validated FI scores.

Follow-up	Success	Fully continence	Failed
6 months	Patients: 167 (65.2%) FI score: 5/24 (0-14)	Patients: 21 (12.5%)	Patients: 89 (34.7%) FI score: 13/24 (7-24)
Medium-term *	Patients: 142 (60.4%) FI score: 5/24 (0-15)	Patients: 27 (11.4%)	Patients: 93 (39.5%) FI score: 13/24 (7-24)
Long-term *	Patients: 115 (62.1%) FI score: 5/24 (0-11)	Patients: 12 (10.4%)	Patients: 70 (37.8%) FI score: 13/24 (7-21)

Table 5. 3: Factors associated with SNM outcomes measures at 6 months. Linear logistic regression: values are 95% Confidence Interval. Incontinence score: St Mark's 24/24; * p value < 0.05 difference statistically significant.

Success at 6 months				
	Odds Ratio	**95% Confidence Interval**		***p* value**
		Lower	**Upper**	
Age	0.9957	0.3408	1.3672	0.6262
Sex (Female)	0.6793	0.3443	1.3400	0.2564
Urge Incontinence	1.7345	0.9158	3.2853	0.0835
Passive Incontinence	0.5052	0.2672	0.9554	*0.0368
Mixed Incontinence	1.1038	0.6574	1.8533	0.7090
Baseline score	1.1255	1.0539	1.2019	*0.0003

Table 5. 4: Factors associated with SNM outcomes measures at medium-term follow up. Linear logistic regression: values are 95% Confidence Interval. Incontinence score: St Mark's 24/24; * p value < 0.05 difference statistically significant.

Success at medium-term follow up				
	Odds Ratio	**95% Confidence Interval**		***p* value**
		Lower	**Upper**	
Age	0.9904	0.9731	1.0079	0.2792
Sex (Female)	0.8460	0.4291	1.6680	0.6277
Urge Incontinence	1.2396	0.6651	2.3104	0.4966
Passive Incontinence	0.8903	0.4548	1.7428	0.7351
Mixed Incontinence	0.9590	0.5649	1.6280	0.8768
Baseline score	1.1672	1.0885	1.2516	*0.0000

Table 5. 5: Factors associated with SNM outcomes measures at long-term follow up. Linear logistic regression: values are 95% Confidence Interval. Incontinence score: St Mark's 24/24; * p value < 0.05 difference statistically significant.

Success at long-term follow up				
	Odds Ratio	**95% Confidence Interval**		***p* value**
		Lower	**Upper**	
Age	0.9828	0.9636	1.0024	0.0824
Sex (Female)	0.7672	0.3648	0.6136	0.4812
Urge Incontinence	0.6375	0.3197	1.2711	0.2026
Passive Incontinence	0.9333	0.4496	1.9375	0.8533
Mixed Incontinence	1.4076	0.7754	2.5517	0.2612
Baseline score	1.3037	1.1891	1.4293	*0.0000

5.3.1.4 Outcome after treatment failure

Twelve patients (4.6%) of the 256 patient cohort had a poor outcome (lack of efficacy) at the first post-operative follow up 21/24 (19-24). Deterioration in St Mark's FI scores were noted for 9 patients despite multiple stimulation parameter changes. These patients had the SNM device removed. The remaining 3 patients had lead misplacement or migration which was surgically corrected with a good ultimate outcome (median St Mark's Score: 5/24) (5-10).

5.3.1.5 Battery changes

Of the 185 patients interviewed at the last follow up, 121 patients (65.4%) underwent at least one battery change, with 48 of these (39.6%) having two battery changes. There were further 6 (5%) patients with post-operative wound infections; 4 of these 6 patients healed with a full course of antibiotics, 2 had the SNM removed.

5.3.1.6 Complications

Of the 256-total cohort of patients, 61 patients had recorded complications (23.8%). Eleven patients (4.2%) had the SNM implant removed for complications rather than treatment failure, 14 (5.4%) had other forms of revision surgery, 36 (14%) were successfully treated conservatively and 51 patients (19.9%) required a change of their SNM stimulation parameters (Table 5.6). Wound infection/implant rejection affected 14 patients (5.4%). Of these, 3 patients responded to oral antibiotic therapy, while 7 required SNM removal. Local chronic pain/numbness, including pain radiating to the leg, was reported by 30 patients (11.7%), minor post-operative bleeding was recorded in 8 patients (3.1%).

Table 5. 6: A summary of SNM complications and the overall complications treatments from a total cohort of 256 patients is shown here.

Total complications	*61 patients (23.8%)*	**Overall complications treatment**	*61 patients (23.8%)*
Failure	*9 patients (3.5%)*	SNM explantation	*11 patients (4.2%)*
Infection	*14 patients (5.4%)*	Revisional surgery	*14 patients (5.4%)*
Pain/Numbness	*30 patients (11.7%)*	Conservative treatment	*36 patients (14%)*
Bleeding	*8 patients (3.1%)*	Change of setting	*51 patients (19.9%)*

5.3.2 Sphinkeeper: first multicentre experience in the UK

Between 2016 and April 2019, 27 patients underwent the Sphinkeeper procedure; 19 at RLH and 8 at SMH.

5.3.2.1 Demographics

The patient total group (BARTS and SMH) consisted of 9 males and 18 females; their median age was 57 years (Range 27 - 87 years). The median BMI was 29 (23 - 34), 44% (12/27) had previous pelvic floor surgery and 56% (10/18) of female patients had prior obstetric injury in the past.

Of the 27 patients, 75% had had symptoms of FI for more than 2 years, and all patients had exhausted other conservative treatments. Five patients had undergone an initial trial of sacral nerve stimulation that had failed. Seventy-eight percent (21/27) of patients suffered from mixed symptoms of faecal incontinence (i.e. urge and passive in nature), while 22% (6/27) suffered from passive faecal incontinence in isolation. Median preoperative St Mark's FI score was 15/24 (11 - 24).

Preoperative EAUSS showed degeneration or disruption of the internal anal sphincter in 12 of the 27 patients (44%), and disruption of the external anal sphincter in 10 of 27 patients (37%). Resting pressures were attenuated (hypotonia) in 17 patients (63%); squeeze pressures and endurance squeeze were attenuated (hypocontractility) in 6 patients (22%). The median length of the anal canal was 3.4 cm (2.3 – 4.6 cm). The baseline patient characteristics of the study cohorts in each hospital are listed in Table 5.7.

Table 5. 7: Demographics and baseline characteristics excreted retrospectively form a retrospective database in two major tertiary centres in the UK.

	BARTS group **N = 19**	**SMH group** **N = 8**
Male/Female	7/12	2/6
Age, median (IQR)	57 (51-67)	64 (54-73)
BMI, median (IQR)	29 (26-32)	27(24-33)
Previous pelvic floor surgery, % (n)	52 (10/19)	25 (2/8)
Obstetric injury, % (n)	50 (6/12)	66 (4/6)
ASA I/II/III/IV	2/15/2/0	3/4/1/0
EAUSS: IAS defect or degeneration, % (n) **EAUSS: EAS defect or degeneration, % (n)**	47 (9/19) 52 (10/19)	38 (3/8) 0 (0/8)
Length anal canal, median (cm)	3.2 (2.1-4.1)	3.1 (2.0-5)
Reduced resting pressure, % (n)	52 (10/19)	87.5 (7/8)
Reduced squeeze pressure, % (n)	26 (5/19)	12.5 (1/8)

5.3.2.2 Operative experience and postoperative complications

At BARTS, 19 consecutive patients were treated with the placement of SphinKeeper prostheses under digital guidance. In 10 procedures, the device was noted to misfire for technical reasons intraoperatively. In these cases a new device was used to complete the procedure. At SMH, in which prostheses were placed under ultrasound guidance during surgery, difficulties with device misfire also occurred, although the number of occasions this happened was not recorded.

The median intraoperative time for the SphinKeeper procedure in the whole cohort was 35 minutes (30 - 55 minutes). There were no intraoperative complications other than device misfire. All patients at BARTS were discharged on the same day, with a few patients at SMH staying overnight for social reasons. There were no readmissions within 30 days of surgery; however, 2 patients returned to the emergency department because of perianal pain and bloody discharge, which was managed conservatively with oral antibiotics and analgesia in both cases.

5.3.2.3 Follow up

All patients were followed up at least once in the outpatient department within 3 months of surgery. No significant postoperative complications were reported by any of the patients at that time point. Patients continued to receive outpatient review as clinically necessary. Median follow-up of the whole cohort was at 12 months (3 – 26). St Mark's FI score at follow-up significantly improved from baseline (median -6 points [range -12 to +3]; paired t-test $p < 0.00016$) with 14/27 (51.9%) patients achieving a ≥ 50% reduction in SMIS. Eight patients (29.7%) had no improvement or a worsening (increase) in score after implant.

5.3.2.4 Postoperative imaging

Postoperative imaging was carried out in 26 / 27 patients (one patient declined radiological follow-up). Of the patients who had postoperative imaging, 20 underwent EAUSS and 5 underwent MRI. The radiological modality was different depending on the single centre availability. In one patient who presented with abdominal pain to the emergency department seven months after surgery, a CT of the pelvis was carried out and this was used as postoperative radiological follow-up for the SphinKeeper procedure.

Despite the SphinKeeper procedure aiming to insert 10 prostheses (i.e. 10 firings of the device), a median of 7 prostheses (range 0 – 10) were visualised per patient in the postoperative imaging scans (Table 5.8; Figures 5.5 & 5.6). Of those visualised, a median of 5 (range 0 - 10) were ideally placed. There was no obvious relationship between number of optimally placed prostheses and outcome based on reduction in St Mark's FI score (Table 5.9 and Fig. 5.7). Thus in the 48% patients (n =14) with significant improvement in SMIS, the median number of prosthesis visualised was 10 (6 – 10), and of these, a median of 5 (1 – 10) were placed in an ideal position. In the 12 patients without a 50% reduction in St Mark's FI score, the median of prosthesis visualised was also 7 (0 – 10) with a median of 5 prostheses (1 – 8) optimally placed, Chi2 test: p = 0.79.

Median postoperative St Mark's FI score did not vary by centre (BARTS: 10/24 (3 - 22) vs. SMH: 10/24 (5 - 17), p = 0.912) but median number of visualised prostheses was slightly higher at SMH (BARTS: 7 (0 - 10) vs. SMH 9 (7 - 10), p = 0.056). Five patients implanted at BARTS had substantially fewer prostheses seen in the postoperative imaging than would be expected

(median 3, range 0 – 6), whereas at SMH, the number of prosthesis identified by the postoperative imaging was always greater than 7 (median 9, range 7 - 10).

Table 5. 8: St Mark's FI scores (SMIS) and results of postoperative imaging at SMH and BARTS. NA = patient lost in the follow up; * = ≥ 50% reduction in St Mark's FI scores (n = 14; defines success). Summary shows Median and Range.

	SMIS			Radiological prosthesis location			
Hospital	**Pre-operative**	**Post-operative**	**Change**	**Modality**	**Total prostheses visualised**	**Ideal placement**	**Sub-optimal placement**
SMH	21	10	-11*	EAUSS	10	8	2
SMH	15	11	-4	MRI	7	6	1
SMH	15	10	-5	MRI	7	5	2
SMH	18	7	-11*	EAUSS	10	7	3
SMH	21	17	-4	CT	10	8	2
SMH	11	5	-6*	MRI	10	3	7
SMH	15	15	0	MRI	8	8	2
SMH	17	7	-10*	MRI	8	6	2
BARTS	14	17	3	EAUSS	6	5	1
BARTS	18	15	-3	EAUSS	3	0	3
BARTS	11	11	0	EAUSS	6	3	3
BARTS	18	6	-12*	EAUSS	7	4	3
BARTS	14	5	-9*	EAUSS	7	1	6
BARTS	20	10	-10*	EAUSS	10	9	1
BARTS	12	5	-7*	EAUSS	6	5	1
BARTS	15	18	3	EAUSS	7	2	5
BARTS	18	18	0	EAUSS	3	1	2
BARTS	14	5	-9*	EAUSS	6	1	5
BARTS	12	4	-8*	EAUSS	6	6	0
BARTS	16	17	1	EAUSS	0	0	0
BARTS	22	10	-12*	EAUSS	10	5	5
BARTS	12	3	-9*	EAUSS	9	3	6
BARTS	14	7	-7*	EAUSS	10	10	0
BARTS	24	22	-2	EAUSS	9	7	2
BARTS	11	12	1	EAUSS	7	5	2
BARTS	11	13	2	NA	NA	NA	NA
BARTS	18	8	-10*	EAUSS	10	8	2
Summary	15 (11-24)	10 (3-22)	-6 (-12 to +3)	-	7 (0-10)	5 (0-10)	2 (0-7)

Table 5. 9: Contingency table showing no relationship between numbers of optimally-placed prostheses and outcome based on ≥ 50% reduction in SMIS score. Chi2 test: p = 0.79.

	≥ 50% SMIS	**< 50% SMIS**	**Marginal rows totals**
≥ 50% ideal placement	10	8	18
< 50 % ideal placement	4	4	8
Marginal columns total	14	12	26

Figure 5. 5: Post-operative EAUSS. **a.)** Postoperative EAUSS in a patient with ideal placement of the prostheses in the intersphincteric plane in the mid-anal canal. **b.)** Horizontal dislodgement of the intersphincteric prostheses in the distal anal canal.

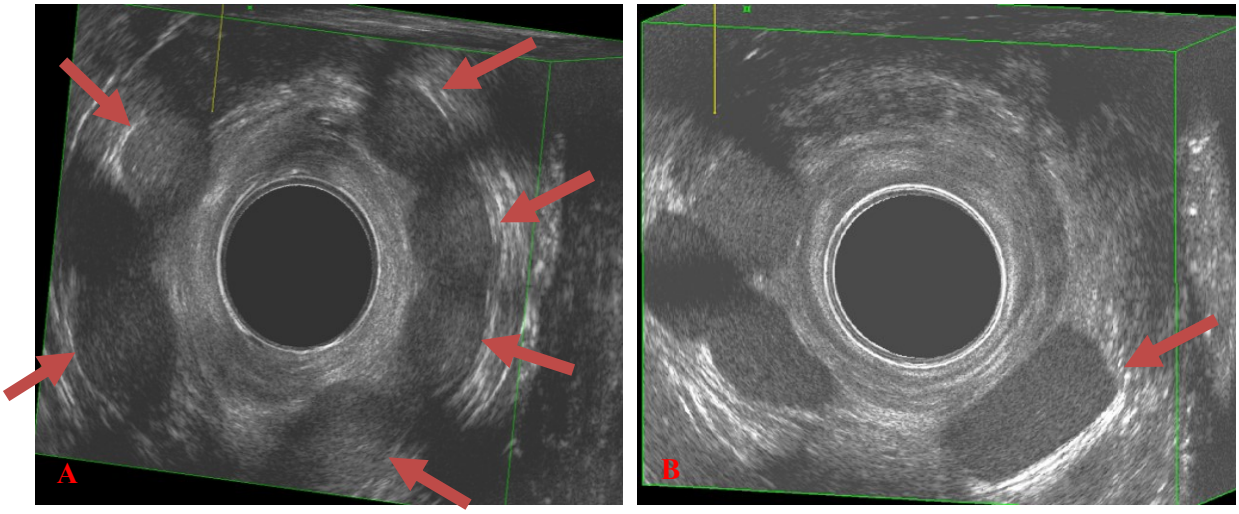


Figure 5. 6: Post-operative MRI. **a.)** Intersphincteric placement of prostheses, however gaps are demonstrated. Also, one prosthesis has partially traversed the levator plane posteriorly. This patient was implanted under intra operative guidance with EAUSS. **b.)** Successfully intersphincteric placement of prostheses, however some of the prostheses migrated distally.

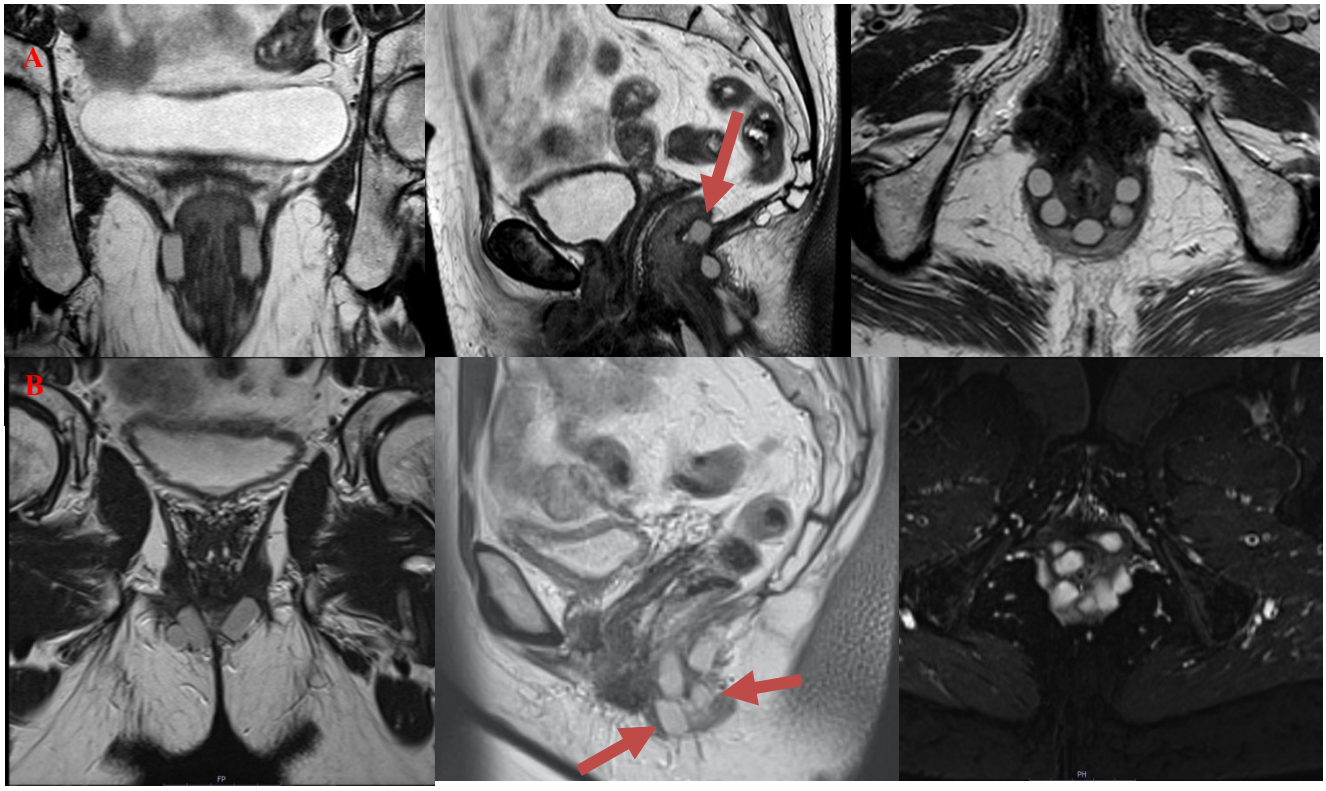
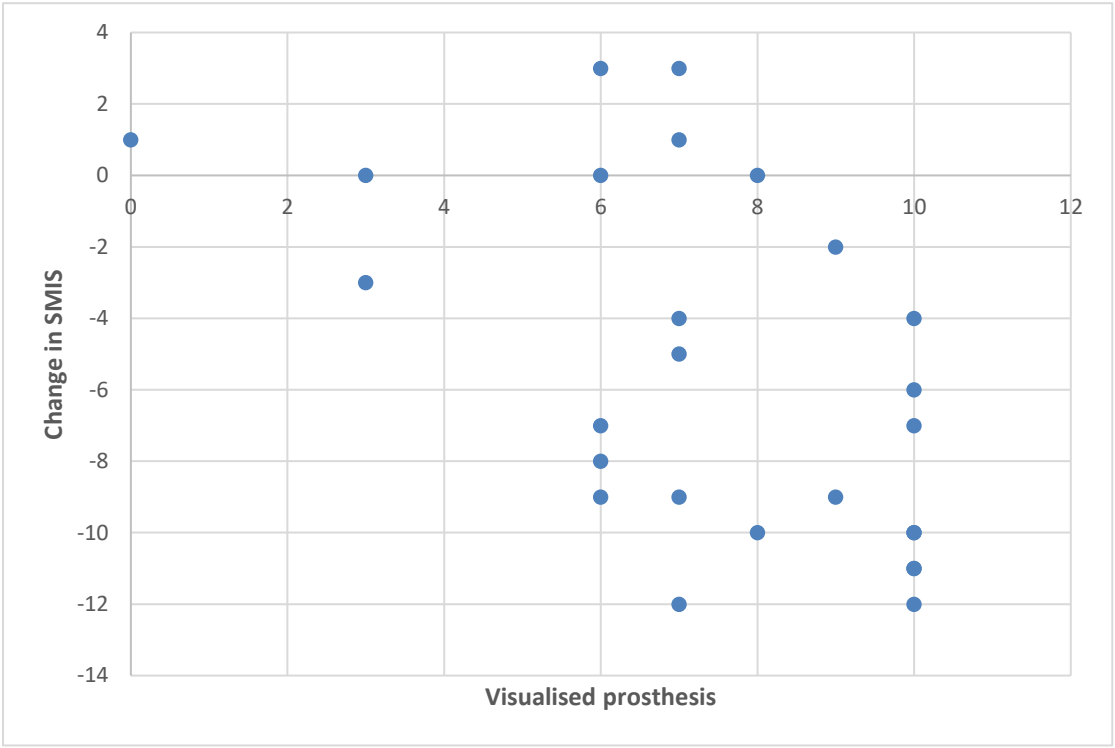
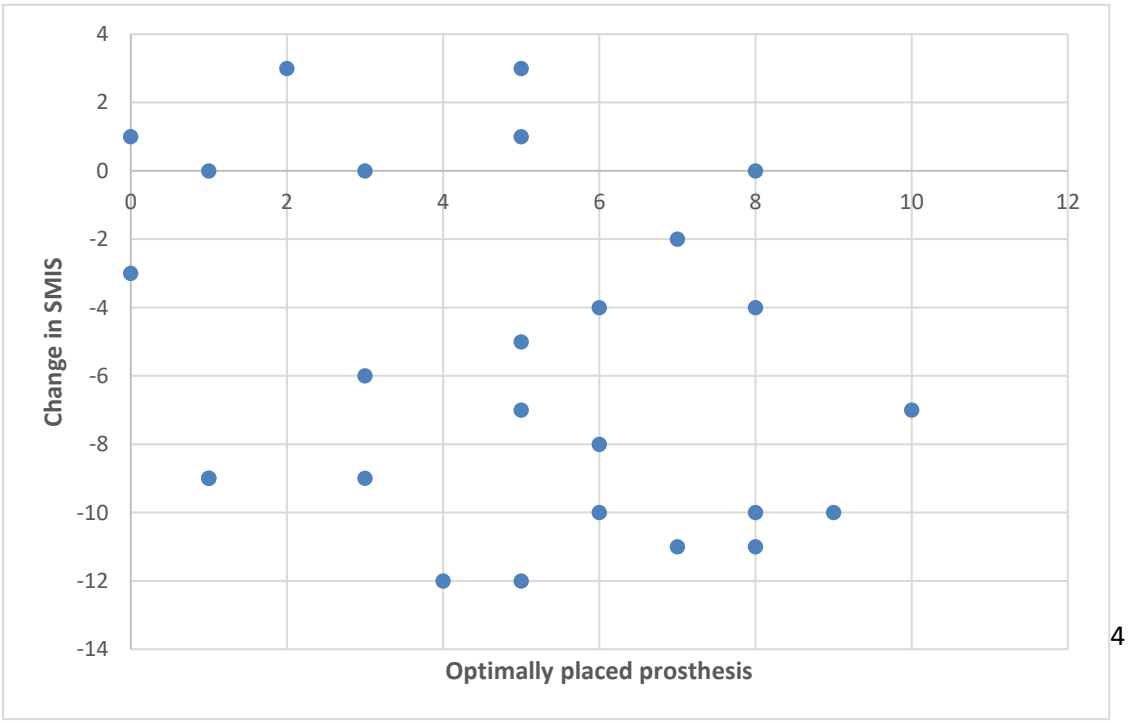


Figure 5. 7: a.) Correlation between change in SMIS score and the total number of prostheses visualised. b.) Correlation between change in SMIS score and the total of ideally-placed prostheses.

A)



B)



5.4 Discussion

This first study demonstrates that SNM significantly improves FI score for approximately 63% of patients at the medium-term follow up point. At long-term follow up, a significant improvement was again recorded for almost 60% of patients. To the best of our knowledge, these data are the longest published results of functional outcome measures after SNM for FI. The median follow-up for this study was 11 years (132 months), with the longest individual followed-up over 22 years (264 months).

The extended follow-up of this study and its prospective data collection allows an estimation to be made of the long-term efficacy of SNM for FI. However, there are several limitations that affect our analyses. Despite the prospective nature of this study there were significant time gaps in the data contained in our database which resulted in a smaller cohort of patients being eligible for inclusion in this study than the total number that will have been treated by our centre. A lack of recorded bowel diary data for patients who had a SNM implanted also meant that change in frequency of incontinent episodes, urgency and quality of life data could not be accurately measured and thus these analyses have been omitted. A further limitation was that only 72% (n = 185) of patients were contactable for long-term follow up. Also, there was lack of important other data recorded in the database, such as previous treatments patients had received. The final functional outcome measures for those who failed PNE or had their SNM devices removed are unknown as most of the patients have been lost to follow up.

Other studies have reported SNM outcome measures in the medium to long term. In 2015 Altomare and colleagues in a European multicentre SNM outcome group reported results of 228 patients after a median of 84 months follow up (101). They reported that success was

maintained in 71% of cases with a range across centres of 65 – 80% and full continence achieved in 50% of the cohort (101). This work followed previously published results again by Altomare *et al*., where continence was reported to improve by 50% or greater for 74% of their total cohort at 74 months (60 – 122) post implant (108).

In the data presented by this study I did not observe a resumption of full continence in a similar percentage of patients to Altomare *et al*. However, the reduction of incontinence scores and complication rates were similar to Altomare *et al* and in line with other published studies (170,184,185). Of note, data from our group published by Hollingshead *et al* in 2011 reported that 83% of a small patient cohort were still deriving benefit from SNM, with a significant reduction in FI scores over a 10 year follow up period (120 – 138 months) (176). Nevertheless, the data reported in my study suggest improvements are not sustained in the longer-term for more than 60% of patients.

Although the presented outcome data are less impressive than others reported for shorter follow up periods (174,175,186), they are still very encouraging results if compared to other more invasive techniques (sphincter repair, stoma formation, implantation of artificial bowel sphincter) (122–124,131,133,135). SNM has clear advantages over the few available techniques for FI including the fact it can be used for patients with a wide degree of FI causes and with varying degrees of severity. Technical problems are infrequent and there is overwhelming evidence that the complication rate is low. For those patients with loss of efficacy in the longer term, the cause for poor function is often not clear. This could be explained by a deterioration of the patient's condition over time or more simply a loss of response to stimulation. When this occurs it should be kept in mind that many patients who

attend clinic may require battery replacement. Furthermore, for some patients, efficacy can be restored by adjusting SNM settings such as amplitude, frequency and pulse width of stimulation (173).

In summary, the data presented by this study indicate that SNM is an effective and durable treatment for FI, with decreased FI scores reported by approximately 60% of all patients in the long term. As such it should be considered for patients with FI after conservative measures have failed. The mechanisms of action that mediate SNM function are complex and multifactorial, and thus future work will be necessary to determine: why not all patients become completely continent; why some initially derive benefit but later report deterioration in function despite SNM optimisation; and, why some patients fall to derive any benefit from PNE or SNM implantation.

The second study in this chapter is a retrospective clinical audit that evaluated the first multicentre experience in the UK with the Sphinkeeper prosthetic implants for treatment of faecal incontinence in a heterogeneous group of patients that had already failed other treatments. The implantation of Sphinkeeper proved to be a safe and feasible procedure, easily performed as a day case, well tolerated in all patients and without any serious complications. The procedure was also relatively simple to perform from a technical point of view. However, surgeons in both hospitals did experience difficulties with the firing of the Sphinkeeper delivery system, which may have caused suboptimal placement of the prostheses. This issue may have also contributed and influenced the clinical outcome: in fact just over half (51.9%) patients showed a clinically meaningful improvement in the St Mark's faecal incontinence scores. Interestingly in the group of patients with a more significant clinical improvement more

prostheses were found in what was considered to be the ideal location by prior publications, i.e. the proximal inter-sphincteric space. The presented data suggests that this location might be the most favourable position for the Sphinkeeper prosthesis.

A notable finding on post-operative imaging in both centres was the unexpected number of prostheses identified, with some absent on imaging that would be expected to be present, in addition to unexpected locations or positions of prostheses in and around the anal canal. Overall the clinical outcome appeared to be similar for patients treated in the two centres; however, the number of prosthesis identified postoperatively in the SMH group, where the use of intraoperative EAUSS was routinely used, was greater. The use of intraoperative ultrasound guidance allows undiagnosed missed firings of the prosthetic to be detected during the procedure, although from the presented data it is clear that this is not sufficient to identify every missed firing. For this reason we would also strongly recommend that every cartridge is inspected after each fire to ensure that the implant has been satisfactory deployed and it is not retained within the delivery system.

Our results in this regard are at odds with the original description of the SphinKeeper technique reported by Ratto *et al* (118), in a prospective study of 10 patients. At 3 months' follow-up, all patients were reported to have 10 prostheses successfully implanted, with all perfectly positioned without any missing or misplaced prostheses. Furthermore, the authors did not report any device misfires or technical difficulty with the delivery system. A subsequent report from La Torre *et al* (182), in a cohort of 13 patients, indicated that only one patient had an anterior displacement of a single prosthesis, prosthesis extrusion occurred in two other patients, and no device misfires were reported (182). Both of these studies used EAUSS guidance intra-

operatively. However, our experience, even in those patients in whom EAUSS guidance was used, was that no patient had a radiological outcome that resembled the images produced by ultrasonographic reconstruction in these previous studies (118,182).

Our results are more akin to those of Litta *et al* (187). Using follow-up EAUSS assessment of prosthetics, they found that the implantation was adequate in only 23 of the 42 patients (based on 6/10 prostheses placed in the target area). The SMIS in their study decreased from a median of 15/24 to 10/24 ($p < 0.001$) i.e. near identical to our study. Using a categorical cut-off in a subgroup of 14 females with sphincter defects, they reported results similar to our own experience i.e. 8 of 14 patients (57%) showed a > 50% reduction in the total number of faecal incontinence episodes per week.

I acknowledge that this clinical audit may have some limitations, mainly related to the heterogeneity of the patients and the lack of prospective standardisation of surgical technique, follow up modality and radiological methods. Yet, despite not being a prospective study, it does reflect everyday clinical practice and highlights potential pitfalls and the clinical outcome measures associated with this procedure. Despite these limitations, this service evaluation has yielded important results that may guide surgeons who consider utilising this new treatment option for patients suffering from faecal incontinence.

5.5 Conclusion

This study demonstrates that SNM is an effective treatment for FI in the long term. SNM results in an improvement of validated FI scores for approximately 60% of all patients in the long-term; however, there is a slight reduction of efficacy over the time due to factors that remain

unclear. It was also demonstrated by this study that Sphinkeeper is a safe and feasible procedure. This could be a valid alternative minimally invasive treatment for those who suffer from faecal incontinence. The use of intraoperative EAUSS should be considered at least until the surgical procedure has become well standardised and the delivery of the implant optimised. Larger prospective multicentre studies should be also considered to further explore the possible clinical indications of the technique and to better understand the long term efficacy of this treatment.

6 Discussion

The aim of my thesis was to improve the assessment and treatment of faecal incontinence (FI). This started with me undertaking a survey to assess support services in the community that are currently available for patients suffering from FI. The rationale for this is that national guidelines have advised the majority of patients should be treated in the community in the first instance (48). In the UK this care is delivered by continence advisors and I sought to conduct an online survey to assess their current scope of practice. Overall, the results of this study suggest that CA provide good care for those with FI, but the service is not optimal and there are several areas which could be improved. The majority of CA reported they are able to confidently perform a digital rectal examination and to diagnose external rectal prolapse. Less than half of the interviewed CA prescribe medication; however, most were not trained to prescribe and relied upon the patient's General Practitioner. The majority of CA seemed happy to advice on basic dietary management. They demonstrated good knowledge regarding the different non-invasive treatments and most of them were happy to recommend anal plugs and / or inserts. Continence advisors considered patient choice to be the most important factor when deciding which continence products to use. Most importantly, three quarters of CA felt they were adequately supported in their practice. However, just over half felt they had received adequate training and that this training needed to be more accessible. This study had some limitations, including the fact that only half of the approached CA responded. Therefore, these results may reflect the practice of a self-selected group who may be more motivated. An online survey was a useful approach to gather responses from all around the country, but this may discouraged those who did not regularly use email. This study has highlighted that there may

be a role for the development of a targeted training programme for CA in the future. However, thought should be given to what should be taught and how this service should be delivered.

My next set of studies aimed to improve the diagnosis and assessment of FI in secondary care and to overcome the limitations of more established anal manometry devices. The first of these studies was designed to obtain the first normative values for the new Anopress manometry device. To the best of my knowledge this study was one of the largest reported series of normal values for anal manometry for asymptomatic subjects in the published literature. As has already been reported by previous studies for prior manometry devices, differences were observed between the subgroups in this study cohort. Interestingly, the normative values for the Anopress device were lower than the values used for water perfused manometry equipment. This is likely due to technological differences. The Anopress records values from the whole of the anal canal rather than conventional devices which record the maximum values identified at discrete points along the length of the canal. It is hoped that the ability of the Anopress device to assess the entire anal canal function may allow better correlation of ARP tests and symptoms in future. In the second Anopress study, statistically significant reductions in all of the measured ARP parameters were demonstrated for patients with symptomatic FI. This suggests that the Anopress device was able to detect impaired sphincter function in those with symptomatic FI. It should be remembered that the cohort evaluated by that study was small and very few men were recruited. The final Anopress study was a prospective observational analysis which demonstrated a strong correlation between the manometric measurements of the current standard of care high-resolution water perfused manometry and the newer Anopress. The r^2 values were 0.84 for resting pressure, 0.97 for voluntary squeeze increment, 0.90 for endurance of voluntary squeeze, 0.96 for involuntary squeeze increment, and 0.91 for strain pressure (all

$p < 0.001$). The qualitative analysis demonstrated that the Anopress may have overcome many of the disadvantages of water perfused manometry. Particularly, it was noted that the Anopress is smaller in size, lighter in weight, and has wireless technology to transmit results to a computer. Also, the preparation and calibration of the Anopress catheter were much easier and faster. Furthermore, the Anopress system is less expensive than the water perfused manometry technology. Finally, the Anopress was better tolerated by patients, who reported lower scores for pain and discomfort. Limitations of this newer technology were also observed and reported. These include the inability to measure the length of the anal canal and to measure the rectal capacity with the catheters that were commercially available at the time of the study.

I undertook an evaluation of novel non-invasive treatments for FI. The first study took the form of assessing the effect of the Renew anal insert on clinical practice. A significant improvement in St Mark's Incontinence Scores was seen with the use of Renew anal insert at short-term follow up (median 11 weeks) for patients with passive FI ($p < 0.0001$). Approximately 80% of patients reported that they liked this non-invasive treatment and more than half experienced a subjective improvement in symptoms. The Renew device also appears to be well tolerated, as it is soft and comfortable. It seems that this newer treatment may have overcome some of the disadvantages of the more established anal inserts (85,188). This study was limited by the fact that it was a small retrospective single institution series with a short follow up.

This study was followed by a single blind pilot randomized controlled trial to compare the Renew anal insert and percutaneous tibial nerve stimulation (PTNS). This demonstrated a degree of reduction in episodes of faecal incontinence for the all Renew group (100%), versus

88% in the PTNS group ($p = 0.074$). A ≥ 50% reduction in episodes of faecal incontinence was achieved in 75% of the Renew group and 48% of the PTNS group ($p = 0.041$). After three months of treatment, the median number of episodes of faecal incontinence was not statistically different between the two treatment groups ($p = 0.086$). When compared with baseline figures, the Renew group had significantly better outcomes than the PTNS group for St Mark's FI ($p = 0.001$), ICIQ-B bowel pattern ($p = 0.001$), ICIQ-B bowel control ($p = 0.001$) and ICIQ-B quality of life ($p = 0.001$) scores. The results of this study suggest that the Renew insert could be an attractive alternative to PTNS for patients with FI who have failed other conservative treatments. Another advantage of the Renew anal insert over PTNS is that the patient can apply the insert at home and they do not have to attend hospital on a weekly basis. This could save time and money for both the patient and the National Health Service. The major strength of this study is the prospective randomized design and the double-blind fashion in which the results were analysed. Furthermore, to the best of my knowledge this randomized trial is the first study that has directly compared the Renew anal insert to PTNS. A significant limitation is the relatively small sample size. Given the paucity of objective prospective studies assessing the effect of the Renew insert for patients with FI, no realistic sample size calculation could be performed. Because of this, the sample study size was limited to 50 patients by the medical ethical committee prior to commencement of the trial. It is important to highlight that only short-term follow-up data are presented by this study and while the long-term results from PTNS have already been widely demonstrated, it is not clear if patients will continue to use the Renew insert on a long-term basis.

My next set of studies assessed more invasive treatments for FI. The first of these studies was a review of outcome data and demonstrated that SNM significantly improves FI score for approximately 60% of patients at medium-term follow up (median 110 months) point, with a median St Mark's FI score of 10/24 ($p < 0.001$) when compared to the baseline. At long-term follow up (median 132 months), a significant improvement was again recorded for 62% of patients who could be contacted at that time point. These patients had a median St Mark's FI score of 10/24 (0 – 21; $p < 0.001$) when compared to the baseline. To the best of my knowledge, these data are the longest published follow up results of functional outcome measures after SNM for FI. The median follow-up for this study as a whole was 11 years, with the longest individual being followed-up for over 22 years. There were limitations to this study, the most significant of which was that there were significant gaps in the institutional database that resulted in not all of the patients treated by our centre being identified for inclusion in this study. There was also a lack of recorded bowel diary data for the study patients, which meant that change in frequency of incontinent episodes, urgency and quality of life data could not be accurately measured or analysed. The data presented by this study demonstrate that full continence resumed in only 10% of patients, which is substantially lower than rates reported by other studies (101,108,177,189,190). Nevertheless, the reduction of FI incontinence scores and complication rates reported in my study are in keeping with published reports (101,108,189). Although the functional outcome data reported in this thesis are less impressive than those reported by other authors over shorter follow up periods, they remain very encouraging results when compared to other previously reported invasive techniques (sphincter repair, stoma formation, implantation of artificial bowel sphincter) (107,169,191,192). Moreover, it should be taken into consideration that SNM has clear advantages over the few other available techniques, especially given its efficacy for a wide range of indications and

degrees of FI severity. As such, these data support the continued use of SNM for patients with FI after conservative measures have failed.

The second of my studies assessing more invasive treatments for FI was the first UK multicentre evaluation of Sphinkeeper prosthetic implants. This was a retrospective study assessing a heterogeneous group of patients with FI that had already failed other standard treatments. The implantation of Sphinkeeper proved to be a safe and feasible procedure, easily performed as a day case, well tolerated in all patients and without any serious complications. Approximately half of the patients (about 50%) reported significant improvement with the median St Mark's score at last follow up of 10/24, which represented a significant reduction from the baseline scores ($p < 0.001$). However, surgeons in both centres performing these procedures did experience difficulties with the firing of the Sphinkeeper delivery system, which may have caused suboptimal placement of the prostheses. This issue may have influenced the observed clinical outcome. The results of this study are also quite different from those reported by two other published pilot studies where all prostheses were successfully implanted and there were no device misfires or technical difficulties with the delivery system (118,182). The results of this study call into question the reports of previously published pilot studies and may better reflect everyday clinical practice, in addition to highlighting potential pitfalls and the clinical outcome measures which might be expected from this procedure. Furthermore, this study yielded important results which may guide surgeons who consider utilising this new treatment option for patients suffering with FI.

7 Future work

It was discussed in Chapter 6.1 that SNM is an established treatment for faecal incontinence. Even though SNM is a minimally invasive procedure, which offers significant symptom improvement, some patients experience adverse stimulation effects such as pain and discomfort. This can occur immediately after implantation or during ongoing treatment. Pain and discomfort in the legs and pelvis during SNM may be due to stimulation of adjacent nerves and/or muscles around the electrode. It may also be due to fibrosis developing around the electrode and the device, which may change the size and field of stimulation. The first step following adverse stimulation is to review and change stimulation settings if appropriate. This could result in loss of therapeutic efficacy, discontinuation of therapy and, in some cases, removal of the device (173,193). Currently, little is known about the spread of the electric current from the SNS lead and its effect on adjacent tissues. Thus, programming is done largely on a 'trial and error' basis. At the same amplitude, monopolar stimulation spreads much further than bipolar. Small adjustments in the relative distance and angle between the activated electrodes and the different tissue types can change the shape of the induced electric field.

Diffusion tensor imaging (DTI) is a non-invasive MRI technique that uses anisotropic to estimate the axonal (white matter) organization within the body. This is often used with fibre tractography (FT) which is a three-dimensional radiological reconstruction technique to assess neural tracts using data collected by DTI. Together these two radiological techniques enable visualisation of the pathways and integrity of nerves (194–196) (Fig. 8.1). Limitations of these

techniques in clinical practice include false positive (tracking paths that do not exist) and false negative (not adequately tracking paths that exist) results. Therefore, the interpretation of tractographic reconstructions requires a lot of experience and knowledge (197). Other limitations include the inability to distinguish the direction of the neural pathway (afferent from efferent projections), to determine its function and to identify the presence of synapses along the course of the same neural pathway (197).

It would be interesting to study DTI imaging further as this could provide both structurally and functionally nerve evaluation and therefore could become a first line non-invasive assessment prior to SNS implant. Future works should focus on this new technological aspect and perhaps combine this with a computation model that could help to predict the correct SNS settings during stimulation therapy.

8 Conclusion

In this thesis, I have used novel studies to investigate the diagnosis, assessment and treatment of FI.

8.1 Current available support in the community

I have demonstrated that continence advisors are an important part of the management of FI in the community and that while they are able to utilise many of the current treatments, there is room for improvement. This may be achieved by focused and more easily accessible training.

8.2 Improving patient diagnosis and assessment with a new portable manometric device

Normal range values for the new portable manometric device Anopress have been reported for the first time. Also, it has been demonstrated that the Anopress device appears to detect anal sphincter dysfunction in those with symptomatic FI. Most importantly, Anopress measurements correlate strongly with water perfused manometry. Anopress appears to be better tolerated and also to overcome some of the limitations of older technologies. The Renew device appears to be a safe, well tolerated and effective non-invasive treatment for passive FI.

8.3 Evaluation of novel non-invasive treatments

The randomized trial suggests that both the Renew device and PTNS are effective treatments for FI, although the Renew inserts may be more effective than PTNS. However, only half of the study population would be willing to use these in the longer term.

8.4 Evaluation of invasive treatments

SNS was confirmed as an effective treatment for FI even in the long term, and I have demonstrated this results in an improvement of validated FI scores for approximately 60% of all patients reviewed at 11 years post implantation. However, there was also a slight reduction of SNS efficacy over the time due to factors that remain unclear. Sphinkeeper was demonstrated to be a safe and feasible alternative procedure for FI. The use of intraoperative EAUSS for Sphinkeeper should be considered at least until the surgical procedure has become well standardised and the delivery of the implant optimised. Larger prospective multicentre studies should be also considered to define the clinical indications for this technique and to better understand the long term efficacy of Sphinkeeper treatment.

9 Bibliography

1. La Torre F, Coletta D, Costanzo F, Iaquinandi F, Velluti F. Anorectal anatomy and physiology. Childbirth Trauma. 2016;30(1):15–30.
2. Pick BP. Gray's Anatomy. Vol. 2, British Medical Journal. 1958. p. 801.
3. Netter FH. Atlas of Human Anatomy, Professional Edition. 2018th ed. Netter F, editor. Netter Basic Science. Elsevier; 2011. 204 p.
4. Marcio J, Jorge N, Wexner SD. Anatomy and physiology of the rectum and anus. Vol. 163, European Journal of Surgery. 1997. p. 723–31.
5. Bharucha AE, Blandon RE, Lunniss PJ, Scott SM. Anatomy and physiology of continence. In: Ratto C, editor. Fecal Incontinence: Diagnosis and Treatment. 2007th ed. Springer-Verlag Mailand; 2007. p. 3–12.
6. KenHub. Kenhub [Internet]. 2020 [cited 2020 Jun 1]. Available from: https://www.kenhub.com/
7. Madoff RD, Parker SC, Varma MG, Lowry AC, Mellgren A, Jensen L, et al. Faecal incontinence in adults. Lancet. 2004;14-20;(364(9434)):621–32.
8. Norton C, Whitehead WE, Bliss DZ, Harari D, Lang J. Management of fecal incontinence in adults. Vol. 29, Neurourology and Urodynamics. 2010. p. 199–206.
9. Matzel KE, Bittorf B. Management of fecal incontinence. Semin Colon Rectal Surg. 2016;27(1):15–21.
10. Michael B Chancellor M. Mapping the Future for Incontinence Treatment Worldwide Highlights from the First International Consultation on Incontinence June 28–July 1, 1998, Monaco. Rev Urol. 1999;1(3):(Summer):145–147.
11. Matzel KE. Faecal Incontinence. In: W. Arnold · U. Ganzer, editor.

Coloproctology. Second edi. Springer; 2017. p. 87–102.
12. Quander C. Prevalence of and factors associated with faecal incontinence in a large community study of older individuals. Am J Gastroenterol. 2005;100((4)):905–9.
13. McGrother CW. Epidemiology of faecal incontinence: A review of population-based studies. In: Becker HD., Stenzl A., Wallwiener D. ZTT, editor. Urinary and Fecal Incontinence: An Interdisciplinary Approach. 2005th ed. Springer, Berlin, Heidelberg; 2005. p. 13–23.
14. Stokes AL, Crumley C, Taylor-Thompson K, Cheng AL. Prevalence of fecal incontinence in the acute care setting. J Wound, Ostomy Cont Nurs. 2016;43(5):517–22.
15. Bharucha AE, Dunivan G, Goode PS, Lukacz ES, Markland AD, Matthews CA, et al. Epidemiology, pathophysiology, and classification of fecal incontinence: State of the Science Summary for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) workshop. Vol. 110, American Journal of Gastroenterology. 2015. p. 127–36.
16. Nelson R, Furner S, Norton N, Cautley E. Community-Based Prevalence of Anal Incontinence. JAMA J Am Med Assoc. 1995;274(7):559–61.
17. Milson I. Epidemiology of Urinary incontinence and other lower urinary tract symptoms, pelvic organ prolapse and anal incontinence. In: Abram, Paul. Cardozo, Linda. Wagg, Adrian. Wein A, editor. Incontinence. 6th Editio. Tokyo; 2017. p. 1–142.
18. Macmillan AK, Merrie AEH, Marshall RJ, Parry BR. The prevalence of fecal incontinence in community-dwelling adults: A systematic review of the literature. Dis Colon Rectum. 2004;47(9):1341–9.
19. Ng KS, Sivakumaran Y, Nassar N, Gladman MA. Fecal incontinence:

Community prevalence and associated factors - A systematic review. In: Diseases of the Colon & Rectum. 2015. p. 1194–209.

20. Pretlove SJ, Thompson PJ, Toozs-Hobson PM, Radley S, Khan KS. Does the mode of delivery predispose women to anal incontinence in the first year postpartum? A comparative systematic review. Vol. 115, BJOG: An International Journal of Obstetrics and Gynaecology. 2008. p. 421–34.
21. Ditah I, Devaki P, Luma HN, Ditah C, Njei B, Jaiyeoba C, et al. Prevalence, Trends, and Risk Factors for Fecal Incontinence in United States Adults, 2005-2010. Clin Gastroenterol Hepatol. 2014;12(4):636–43.
22. Rintala RJ, Lindahl H. Is normal bowel function possible after repair of intermediate and high anorectal malformations? J Pediatr Surg. 1995;30(3):491–4.
23. Largo RH, Gianciaruso M PA. Development of intestinal and bladder control from birth until the 18th year of age. Longitudinal Study. Schweiz Med Wochenschr. 1978;(108:):155-60.
24. Kang HW, Jung HK, Kwon KJ, Song EM, Choi JY, Kim SE, et al. Prevalence and predictive factors of fecal incontinence. J Neurogastroenterol Motil. 2012;18(1):86–93.
25. Worsøe J, Michelsen HB, Buntzen S, Laurberg S, Krogh K. Rectal motility in patients with idiopathic fecal incontinence: A study with impedance planimetry. Dis Colon Rectum. 2010;53(9):1308–14.
26. Madoff RD, Williams JG CP. Fecal incontinence. N Engl J Med. 1992;326((15)):1002-7.
27. Small KA, Wynne JM. Evaluating the Pelvic Floor in Obstetric Patients. Aust New Zeal J Obstet Gynaecol. 1990;30(1):41–5.
28. Townsend DC, Carrington E V., Grossi U, Burgell RE, Wong JYJ, Knowles CH, et al. Pathophysiology of fecal incontinence differs between

men and women: a case-matched study in 200 patients. Neurogastroenterol Motil. 2016;28(10):1580–8.

29. Richter HE, Burgio KL, Clements RH, Goode PS, Redden DT, Varner RE. Urinary and anal incontinence in morbidly obese women considering weight loss surgery. Obstet Gynecol. 2005;106(6):1272–7.
30. Erekson EA, Sung VW, Myers DL. Effect of body mass index on the risk of anal incontinence and defecatory dysfunction in women. Am J Obstet Gynecol. 2008;198(5):596.e1-596.e4.
31. Burgio KL, Richter HE, Clements RH, Redden DT, Goode PS. Changes in urinary and fecal incontinence symptoms with weight loss surgery in morbidly obese women. Obstet Gynecol. 2007;110(5):1034–40.
32. Rao SSC. Pathophysiology of Adult Fecal Incontinence. Gastroenterology. 2004;126(1):14–22.
33. Dietz HP, Wilson PD. Childbirth and pelvic floor trauma. Vol. 19, Best Practice and Research: Clinical Obstetrics and Gynaecology. 2005. p. 913–24.
34. Dudding TC, Vaizey CJ, Kamm MA. Obstetric anal sphincter injury: Incidence, risk factors, and management. Vol. 247, Annals of Surgery. 2008. p. 224–37.
35. Oberwalder M, Connor J, Wexner SD. Meta-analysis to determine the incidence of obstetric anal sphincter damage. Br J Surg. 2003;90(11):1333–7.
36. Lawrence JM, Lukacz ES, Nager CW, Hsu JWY, Luber KM. Prevalence and co-occurrence of pelvic floor disorders in community-dwelling women. Obstet Gynecol. 2008;111(3):678–85.
37. Leigh RJ, Turnberg LA. Faecal incontinence: the unvoiced symptom. Lancet. 1982;319(8285):1349–51.

38. Lunniss PJ, Gladman MA, Hetzer FH, Williams NS, Scott SM. Risk factors in acquired faecal incontinence. J R Soc Med. 2004;97(3):111–6.
39. Pernikoff BJ, Eisenstat TE, Rubin RJ, Oliver GC, Salvati EP. Reappraisal of partial lateral internal sphincterotomy. Dis Colon Rectum. 1994;37(12):1291–5.
40. Del Pino A, Nelson RL, Pearl RK, Abcarian H. Island flap anoplasty for treatment of transsphincteric fistula-in-ano. Dis Colon Rectum. 1996;39(2):224–6.
41. Gorfine SR, Billingham RP. Treatment of benign anal disease with topical nitroglycerin. Dis Colon Rectum. 1995;38(5):453–7.
42. Jóhannsson HO, Graf W PL. Long-term results of haemorrhoidectomy. Eur J Surg. 2002;168((8-9):):485-9.
43. Leo, CA; Chandrasinghe, P; Hodgkinson, JD; Vaizey, CJ; Warusavitarne J. Technical Tips and Tricks of Outpatient Treatments for Hemorrhoids. In: Ratto C, editor. Haemorrhoids. 2nd Edition. Springer; 2018. p. 151–66.
44. Nurko S, Scott SM. Coexistence of constipation and incontinence in children and adults. Best Pract Res Clin Gastroenterol. 2011;25(1):29–41.
45. Read NW, Celik AF, Katsinelos P. Constipation and incontinence in the elderly. Vol. 20, Journal of Clinical Gastroenterology. 1995. p. 61–70.
46. Parks AG, Porter NH, Hardcastle J. The Syndrome of the Descending Perineum. J R Soc Med. 1966;59(6):477–82.
47. Lehur, Paul-Antoine. Wong MTC. Incontinence. In: Phillips, R.K.S. Clark S, editor. Colorectal Surgery. Fifth edit. London: Saunders, London, 1993; 2014. p. 167 183.
48. Royal College of Surgeon U. Commissioning guide : Faecal Incontinence [Internet]. RCS website. 2013 [cited 2018 Nov 6]. p. 1–16. Available from: https://entuk.org/professionals/commissioning/commissioning

49. Association of Continence Advisor. ACA [Internet]. 2019 [cited 2019 May 17]. p. 3. Available from: https://www.aca.uk.com/
50. Thekkinkattil DK, Lim M, Stojkovic SG, Finan PJ, Sagar PM, Burke D. A classification system for faecal incontinence based on anorectal investigations. In: British Journal of Surgery. 2008. p. 222–8.
51. Zorcolo L, Bartolo DCC, Leroi AM. Pathophysiology of faecal incontinence. In: Ratto C., Doglietto G.B., Lowry A.C., Påhlman L. RG, editor. Fecal Incontinence: Diagnosis and Treatment. 1st ed. Springer, Milano; 2007. p. 35–9.
52. Engel AF, Kamm MA, Bartram CI, Nicholls RJ. Relationship of symptoms in faecal incontinence to specific sphincter abnormalities. Int J Colorectal Dis. 1995;10(3):152–5.
53. William E. Whitehead, Ph.D., Arnold Wald, M.D. T, Nancy J. Norton BS. Treatment Options for Fecal Incontinence. Dis Colon Rectum. 2001;44((1)):131–42.
54. Buchanan GN, Nicholls T, Solanki D, Kamm MA. Investigation of faecal incontinence. Hosp Med. 2001;62(9):533–7.
55. Norton C, Cody JD. Biofeedback and/or sphincter exercises for the treatment of faecal incontinence in adults. Cochrane database Syst Rev [Internet]. 2012;(7):CD002111. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22786479
56. Norton C. Behavioral Management of Fecal Incontinence in Adults. In: Gastroenterology. 2004.
57. Vaizey CJ, Carapeti E, Cahill JA, Kamm MA. Prospective comparison of faecal incontinence grading systems. Gut. 1999;44((1)):77-80.
58. Agachan F, Chen T, Pfeifer J, Reissman P, Wexner SD. A constipation scoring system to simplify evaluation and management of constipated

patients. Dis Colon Rectum. 1996;39(6):681–5.
59. Close GC and A, editor. The Bristol stool chart. In: Oxford Handbook of Adult Nursing. 2nd ed. Oxford University Press; 2009.
60. Rockwood TH, Church JM, Fleshman JW, Kane RL, Mavrantonis C, Thorson AG, et al. Fecal incontinence quality of life scale. Dis Colon Rectum. 2000;43(1):9–16.
61. Lam TJ, Felt-Bersma RJF. Clinical examination remains more important than anorectal function tests to identify treatable conditions in women with constipation. Int Urogynecol J Pelvic Floor Dysfunct. 2013;24(1):67–72.
62. Tantiphlachiva K, Rao P, Attaluri A, Rao SSC. Digital rectal examination is a useful tool for identifying patients with dyssynergia. Clin Gastroenterol Hepatol. 2010;8(11):955–60.
63. Carrington E V., Scott SM, Bharucha A, Mion F, Remes-Troche JM, Malcolm A, et al. Expert consensus document: Advances in the evaluation of anorectal function. Nat Rev Gastroenterol Hepatol. 2018;15(5):309–25.
64. Deutekom M, Dobben AC, Terra MP, Engel AF, Stoker J, Bossuyt PM BG. Clinical presentation of fecal incontinence and anorectal function: what is the relationship? Am J Gastroenterol. 2007;(102 (2)):351–61.
65. Cho H-M. Anorectal Physiology: Test and Clinical Application. J Korean Soc Coloproctol. 2010;26(5):311.
66. Kim J-H. How to Interpret Conventional Anorectal Manometry. J Neurogastroenterol Motil. 2010;16(4):437–9.
67. Cheeney G, Nguyen M, Valestin J, Rao SSC. Topographic and manometric characterization of the recto-anal inhibitory reflex. Neurogastroenterol Motil. 2012;24(3):e147–e154.
68. Cavazzoni E. Manual of Clinical Anorectal Manometry. Youcanprint;

2016.

69. Vollebregt PF, Rasijeff AMP, Pares D, Grossi U, Carrington E V., Knowles CH, et al. Functional anal canal length measurement using high-resolution anorectal manometry to investigate anal sphincter dysfunction in patients with fecal incontinence or constipation. Neurogastroenterol Motil [Internet]. 2019;31((3)). Available from: https://doi.org/10.1111/nmo.13532
70. Rasijeff AMP, Withers M, Burke JM, Jackson W, Scott SM. High-resolution anorectal manometry: A comparison of solid-state and water-perfused catheters. Neurogastroenterol Motil. 2017;29(11).
71. Kang, HR. Lee, JE. Lee, JS. Lee, TH. Hong, SJ. Kim, JO. Jeon, SR. Kim H. Comparison of high-resolution anorectal manometry with water-perfused anorectal manometry. J Neurogastroenterol Motil. 2015;21(1):126–32.
72. Cuesta MA, D P, Meuwissen SGM. Anal Sensitivity Test : What does it measure and do we need it? Cause or Derivative of Anorectal Complaints ? Dis Colon Rectum. 1997;40(7):811–6.
73. Abdool Z, Sultan AH, Thakar R. Ultrasound imaging of the anal sphincter complex: A review. Br J Radiol. 2012;85(1015):865–75.
74. Maslekar S, Gardiner A, Maklin C, Duthie GS. Investigation and treatment of faecal incontinence. Postgrad Med J. 2006;82(968):363–71.
75. Santoro GA, Di Falco G. Atlas of Endoanal and Endorectal Ultrasonography. 1st ed. Santoro, GA. Di Falco G, editor. Atlas of Endoanal and Endorectal Ultrasonography. Springer; 2004.
76. Walsh KA, Grivell RM. Use of endoanal ultrasound for reducing the risk of complications related to anal sphincter injury after vaginal birth. Vol. 2015, Cochrane Database of Systematic Reviews. 2015.

77. Rao SSC. Diagnosis and management of fecal incontinence. Vol. 99, American Journal of Gastroenterology. 2004. p. 1585–604.
78. Hetzer FH, Andreisek G, Tsagari C, Sahrbacher U, Weishaupt D. MR defecography in patients with fecal incontinence: Imaging findings and their effect on surgical management. Radiology. 2006;240(2):449–57.
79. Enoka RM. Electromyography (EMG). In: Kompoliti, K. Verhagen L, editor. Encyclopedia of Movement Disorders. 1st ed. Elsevier Inc.; 2010. p. 444–6.
80. Oleksy L, Mika A, Kielnar R. Surface Electromiography (Semg) in the Assessment and Treatment of Pelvic Floor Muscles: The Importance of Signal Normalization and Procedure Standardization for Interpretation and Biofeedback. J Nov Physiother. 2017;7(S4).
81. Engel BT, Nikoomanesh P, Schuster MM. Operant Conditioning of Rectosphincteric Responses in the Treatment of Fecal Incontinence. N Engl J Med. 1974;290(12):646–9.
82. Goldenberg, D. Hodges, K. Kathie H. Biofeedback Therapy for Fecal Incontinence. Am J Gastroenterol. 1980;74(4):342–5.
83. Duelund Jakobsen J, Worsoe J, Lundby L, Christensen P, Krogh K. Management of patients with faecal incontinence. Vol. 9, Therapeutic Advances in Gastroenterology. 2016. p. 86–97.
84. Cazemier M, Felt-Bersma RJF, Mulder CJJ. Anal plugs and retrograde colonic irrigation are helpful in fecal incontinence or constipation. World J Gastroenterol. 2007;13(22):3101–5.
85. Doherty W. Managing faecal incontinence or leakage: the Peristeen Anal Plug. Vol. 13, British journal of nursing (Mark Allen Publishing). 2004. p. 1293–7.
86. Coloplast. Peristeen Anal Plug [Internet]. 2019 [cited 2019 Jun 10].

Available from: https://www.coloplast.co.uk/products/bladder-bowel/

87. Deutekom M, Dobben AC. Plugs for containing faecal incontinence. Vol. 2015, Cochrane Database of Systematic Reviews. 2015.
88. How P, Trivedi PM, Bearn PE, Thomas GP. Insert devices for faecal incontinence. Tech Coloproctol [Internet]. 2020;(0123456789). Available from: https://doi.org/10.1007/s10151-020-02317-3
89. Allison M. Percutaneous tibial nerve stimulation for patients with faecal incontinence. Nurs Stand. 2011;25(24):44–8.
90. Wexner SD. Percutaneous tibial nerve stimulation in faecal incontinence. Vol. 386, The Lancet. 2015. p. 1605–6.
91. Hotouras A, Thaha MA, Boyle DJ, Allison ME, Currie A, Knowles CH, et al. Short-term outcome following percutaneous tibial nerve stimulation for faecal incontinence: A single-centre prospective study. Color Dis. 2012;14(9):1101–5.
92. Boyle DJ, Prosser K, Allison ME, Williams NS, Chan CLH. Percutaneous tibial nerve stimulation for the treatment of urge fecal incontinence. Dis Colon Rectum. 2010;53(4):432–7.
93. Thomas GP, Dudding TC, Bradshaw E, Nicholls RJ, Vaizey CJ. A pilot study to compare daily with twice weekly transcutaneous posterior tibial nerve stimulation for faecal incontinence. Color Dis. 2013;15(12):1504–9.
94. Knowles CH, Horrocks EJ, Bremner SA, Stevens N, Norton C, O'Connell PR, et al. Percutaneous tibial nerve stimulation versus sham electrical stimulation for the treatment of faecal incontinence in adults (CONFIDeNT): A double-blind, multicentre, pragmatic, parallel-group, randomised controlled trial. Lancet. 2015;386(10004):1640–8.
95. Horrocks EJ, Thin N, Thaha MA, Taylor SJC, Norton C, Knowles CH. Systematic review of tibial nerve stimulation to treat faecal incontinence.

Vol. 101, British Journal of Surgery. 2014. p. 457–68.

96. Iqbal F, Bokhari S, Tan E, Vaizey CJ. The CONFIDeNT trial. Vol. 387, The Lancet. Lancet Publishing Group; 2016. p. 644.
97. George AT, Maitra RK, Maxwell-Armstrong C. Posterior tibial nerve stimulation for fecal incontinence: Where are we? Vol. 19, World Journal of Gastroenterology. 2013. p. 9139–45.
98. Pandeva I, Biers S, Pradhan A, Verma V, Slack M, Thiruchelvam N. The impact of pelvic floor multidisciplinary team on patient management: the experience of a tertiary unit. J Multidiscip Healthc. 2019;Volume 12:205–10.
99. Hull T, Giese C, Wexner SD, Mellgren A, Devroede G, Madoff RD, et al. Long-term durability of sacral nerve stimulation therapy for chronic fecal incontinence. Dis Colon Rectum. 2013;56(2):234–45.
100. Leroi, AM. Parc, Y. Lehur, PA. Mion, F. Barth, X. Rullier, E. Bresler, L. Michot, F. Gourcerol, G. Parc, R. Lamy, P. Bruley Des Varannes, S. Pimont, S. Meurette, G. Damon, H. Zerbib FE al. Efficacy of sacral nerve stimulation for fecal incontinence: Results of a multicenter double-blind crossover study. Ann Surg [Internet]. 2005;242(5):662–9. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=41567121
101. Altomare DF, Giuratrabocchetta S, Knowles CH, Duyos AM, Robert-Yap J, Matzel KE. Long-term outcomes of sacral nerve stimulation for faecal incontinence. Br J Surg. 2015;
102. Matzel KE, Chartier-Kastler E, Knowles CH, Lehur PA, Muñoz-Duyos A, Ratto C, et al. Sacral Neuromodulation: Standardized Electrode Placement Technique. Neuromodulation. 2017;20(8):816–24.
103. McAlees E, Vollebregt PF, Stevens N, Dudding TC, Emmanuel A V.,

Furlong PL, et al. Efficacy and mechanism of sub-sensory sacral (optimised) neuromodulation in adults with faecal incontinence: Study protocol for a randomised controlled trial. Trials. 2018;19(1):1–19.

104. Jenks J, Hamid R, Shah J, Greenwell T, Ockrim J. 1370 Tined lead versus percutaneous nerve evaluation for sacral nerve stimulator assessment. J Urol. 2013;189(4S).
105. Malouf AJ, Vaizey CJ, Nicholls RJ, Kamm MA. Permanent sacral nerve stimulation for fecal incontinence. Ann Surg. 2000;232(1):143–8.
106. NICE. SNS NICE guidelines. 2004; Available from: https://www.nice.org.uk/guidance/ipg99
107. Wexner SD, Bleier J. Current surgical strategies to treat fecal incontinence. Expert Rev Gastroenterol Hepatol. 2015;9(12):1577–89.
108. Altomare DF, Ratto C, Ganio E, Lolli P, Masin A, Villani RD. Long-term outcome of sacral nerve stimulation for fecal incontinence. Dis Colon Rectum. 2009;
109. Matzel KE. Sacral nerve stimulation for fecal incontinence. In: Anorectal and Colonic Diseases: A Practical Guide to Their Management. 2010. p. 443–52.
110. Watson NFS, Koshy A, Sagar PM. Anal bulking agents for faecal incontinence. Vol. 14, Colorectal Disease. 2012. p. 29–33.
111. Vaizey CJ, Kamm MA. Injectable bulking agents for treating faecal incontinence. Vol. 92, British Journal of Surgery. 2005. p. 521–7.
112. Glasgow SC, Lowry AC. Long-term outcomes of anal sphincter repair for fecal incontinence: A systematic review. Vol. 55, Diseases of the Colon & Rectum. 2012. p. 482–90.
113. Ratto C, Parello A, Donisi L, Litta F, De Simone V, Spazzafumo L, et al. Novel bulking agent for faecal incontinence. Br J Surg.

2011;98(11):1644–52.

114. Luo C, Samaranayake CB, Plank LD, Bissett IP. Systematic review on the efficacy and safety of injectable bulking agents for passive faecal incontinence. Vol. 12, Colorectal Disease. 2010. p. 296–303.
115. Heydari A, Merolla E, Fazlalizadeh R, Giuratrabocchetta S, Piccoli M, Melotti G. Treatment of fecal incontinence with Gatekeeper (TM) implantation. Dis Colon Rectum [Internet]. 2015;58(5):e111. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=71917754
116. Ratto C, Buntzen S, Ganio E, Altomare DF, De La Portilla F, Aigner F. Trials Symposium. Color Dis. 2012;14:68–68.
117. La Torre M, Lisi G, Milito G, Campanelli M, Clementi I. Sphinkeeper™ for faecal incontinence: a preliminary report. Color Dis. 2020;22(1):80–5.
118. Ratto C, Donisi L, Litta F, Campennì P, Parello A. Implantation of SphinKeeperTM: a new artificial anal sphincter. Tech Coloproctol. 2016;20(1):59–66.
119. Fernando RJ, Sultan AH, Kettle C, Thakar R. Methods of repair for obstetric anal sphincter injury. Cochrane Database Syst Rev. 2013;8(12):CD002866.
120. Parks AG, McPartlin JF, Parks AG, McPartlin JF. Late Repair of Injuries of the Anal Sphincter. J R Soc Med. 1971;64(12):1187–9.
121. Fang DT, Nivatvongs S, Vermeulen FD, Herman FN, Goldberg SM, Rothenberger DA. Overlapping sphincteroplasty for acquired anal incontinence. Dis Colon Rectum. 1984;27(11):720–2.
122. Chapman AE, Geerdes B, Hewett P, Young J, Eyers T, Kiroff G, et al. Systematic review of dynamic graciloplasty in the treatment of faecal

incontinence. Br J Surg. 2002;89(2):138–53.

123. Ortiz H, Armendariz P, DeMiguel M, Solana A, Alós R, Roig J V. Prospective study of artificial anal sphincter and dynamic graciloplasty for severe anal incotinence. Int J Colorectal Dis. 2003;18(4):349–54.
124. Devesa JM, Fernandez Madrid JM, Gallego BR, Vicente E, Nuño J, Enríquez JM. Bilateral gluteoplasty for fecal incontinence. Dis Colon Rectum. 1997;40(8):883–8.
125. Romano G, Bianco F, Caggiano L. Artificial bowel sphincter. In: Santoro, G. Wieczorek, A.Bartram PCI, editor. Pelvic Floor Disorders: Imaging and Multidisciplinary Approach to Management. 1st ed. Springer; 2010. p. 341–7.
126. Hajivassiliou CA, Carter KB, Finlay IG. Assessment of a novel implantable artificial anal sphincter. Dis Colon Rectum. 1997;40(6):711–7.
127. Boyle DJ, Murphy J, Hotouras A, Allison ME, Williams NS, Chan CL. Electrically stimulated gracilis neosphincter for end-stage fecal incontinence: The long-term outcome. Dis Colon Rectum. 2014;57(2):215–22.
128. Wexner SD, Baeten C, Bailey R, Bakka A, Belin B, Belliveau P, et al. Long-term efficacy of dynamic graciloplasty for fecal incontinence. Dis Colon Rectum. 2002;45(6):809–18.
129. Rullier E, Zerbib F, Laurent C, Caudry M, Saric J. Morbidity and functional outcome after double dynamic graciloplasty for anorectal reconstruction. Br J Surg. 2000;87(7):909–13.
130. Thornton MJ, Kennedy ML, Lubowski DZ, King DW. Long-term follow-up of dynamic graciloplasty for faecal incontinence. Color Dis. 2004;6(6):470–6.

131. Christiansen J, Lorentzen M. Implantation of artificial sphincter for anal incontinence. Lancet. 1987;330(8553):244–5.
132. Benoist, S. Panis, Y. Michot, F. Coffin, B. Messing B. Artificial sphincter with colonic reservoir for severe anal incontinence because of imperforate anus and short-bowel syndrome: report of a case. Dis Colon Rectum [Internet]. 2005;48(10):1978–82. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=41591395
133. Altomare DF, Dodi G, La Torre F, Romano G, Melega E, Rinaldi M. Multicentre retrospective analysis of the outcome of artificial anal sphincter implantation for severe faecal incontinence. Br J Surg. 2001;88(11):1481–6.
134. Brand MI, Dujovny N. Preoperative considerations and creation of normal ostomies. Clin Colon Rectal Surg. 2008;21(1):5–16.
135. Norton C, Burch J, Kamm MA. Patients' views of a colostomy for fecal incontinence. Dis Colon Rectum. 2005;48(5):1062–9.
136. Perry S, Shaw C, McGrother C, Matthews RJ, Assassa RP, Dallosso H, et al. Prevalence of faecal incontinence in adults aged 40 years or more living in the community. Gut. 2002;50(4):480–4.
137. Volløyhaug I, Mørkved S, Salvesen, Salvesen K. Pelvic organ prolapse and incontinence 15-23 years after first delivery: A cross-sectional study. BJOG An Int J Obstet Gynaecol. 2015;122(7):964–71.
138. Vaizey CJ. Faecal incontinence: Standardizing outcome measures. Color Dis. 2014;16(3):156–8.
139. Moore KH, O'Sullivan RJ, Simons A, Prashar S, Anderson P, Louey M. Randomised controlled trial of nurse continence advisor therapy compared with standard urogynaecology regimen for conservative incontinence

treatment: Efficacy, costs and two year follow up. BJOG An Int J Obstet Gynaecol. 2003;110(7):649–57.

140. Eggertson L. Inspiring confidence to overcome incontinence. Nurse continence advisors help their patients regain control. Can Nurse. 2014;110(7):18–20.
141. NICE. Faecal incontinence The management of faecal incontinence in adults. NICE Guid. 2007;
142. Abrams P, Andersson KE, Birder L, Brubaker L, Cardozo L, Chapple C, et al. Fourth international consultation on incontinence recommendations of the international scientific committee: Evaluation and treatment of urinary incontinence, pelvic organ prolapse, and fecal incontinence. Neurourol Urodyn. 2010;29(1):213–40.
143. Duelund-Jakobsen J, Haas S, Buntzen S, Lundby L, Bøje G, Laurberg S. Nurse-led clinics can manage faecal incontinence effectively: Results from a tertiary referral centre. Color Dis. 2015;17(8):710–5.
144. Allison M. Conservative management of faecal incontinence in adults. Nurs Stand. 2010;24(26).
145. Barleben A, Mills S. Anorectal Anatomy and Physiology. Surg Clin North Am [Internet]. 2010;90(1):1–15. Available from: http://dx.doi.org/10.1016/j.suc.2009.09.001
146. Lee TH, Bharucha AE. How to perform and interpret a high-Resolution anorectal manometry test. J Neurogastroenterol Motil. 2016;22(1):46–59.
147. Coss-Adame E, Rao SSC, Valestin J, Ali-Azamar A, Remes-Troche JM. Accuracy and Reproducibility of High-definition Anorectal Manometry and Pressure Topography Analyses in Healthy Subjects. Clin Gastroenterol Hepatol. 2015;13(6):1143-1150.e1.
148. Vitton V, Ben Hadj Amor W, Baumstarck K, Grimaud JC, Bouvier M.

Water-perfused manometry vs three-dimensional high-resolution manometry: A comparative study on a large patient population with anorectal disorders. Color Dis. 2013;15(12):e726–31.

149. Benezech A, Behr M, Bouvier M, Grimaud JC, Vitton V. Three-dimensional high-resolution anorectal manometry: Does it allow automated analysis of sphincter defects? Color Dis. 2015 Oct 1;17(10):O202–7.
150. Bharucha AE, Stroetz R, Feuerhak K, Szarka LA, Zinsmeister AR. A novel technique for bedside anorectal manometry in humans. Neurogastroenterol Motil. 2015;27(10):1504–8.
151. Rezaie A, Iriana S, Pimentel M, Murrell Z, Fleshner P, Zaghiyan K. Can three-dimensional high-resolution anorectal manometry detect anal sphincter defects in patients with faecal incontinence? Color Dis. 2017;19(5):468–75.
152. THD SpA Italy. THDAnopress [Internet]. 2018 [cited 2019 Mar 26]. Available from: http://thdanopress.com/
153. Carrington E V., Grossi U, Knowles CH, Scott SM. Normal values for high-resolution anorectal manometry: A time for consensus and collaboration. Vol. 26, Neurogastroenterology and Motility. 2014. p. 1356–7.
154. Zbar AP. Reading too much into anal vector volumetric parameters : Correspondence for “anal vector volume analysis: An effective tool in the management of pelvic floor disorders” M. Grande, F. Cadeddu, P. Silveri, P. Ciano, G. M. Attinà, I. Selvaggio, G. Milito. T. Tech Coloproctol. 2011;15(4):473–4.
155. Yang YK, Wexner SD. Anal pressure vectography is of no apparent benefit for sphincter evaluation. Int J Color Dis. 1994;9:92–5.

156. Schizas AMP, Emmanuel A V., Williams AB. Vector volume manometry - methods and normal values. Neurogastroenterol Motil. 2011;23(9):886–92.
157. Grande M, Cadeddu F, Sileri P, Ciano P, Attinà GM, Selvaggio I, et al. Anal vector volume analysis: An effective tool in the management of pelvic floor disorders. Tech Coloproctol. 2011;15(1):31–7.
158. Inc. RM. Renew Anal Insert [Internet]. 2019 [cited 2019 Jun 7]. Available from: https://renew-medical.uk/about-renew-inserts/
159. Giamundo P, Welber A, Weiss EG, Vernava AM, Nogueras JJ, Wexner SD. The Procon incontinence device: a new nonsurgical approach to preventing episodes of fecal incontinence. Am J Gastroenterol. 2002;97(9):2328–32.
160. Norton C, Kamm MA. Anal plug for faecal incontinence. Color Dis. 2001;3(5):323–7.
161. Arroyo-Fernández R, Avendaño-Coy J, Ando-Lafuente S, Martín-Correa MT, Ferri-Morales A. Posterior tibial nerve stimulation in the treatment of fecal incontinence: A systematic review. Vol. 110, Revista Espanola de Enfermedades Digestivas. 2018. p. 577–88.
162. Hotouras A, Murphy J, Walsh U, Allison M, Curry A, Williams NS, et al. Outcome of percutaneous tibial nerve stimulation (PTNS) for fecal incontinence: A prospective cohort study. Ann Surg. 2014;259(5):939–43.
163. Thomas GP, Dudding TC, Rahbour G, Nicholls RJ, Vaizey CJ. A review of posterior tibial nerve stimulation for faecal incontinence. Vol. 15, Colorectal Disease. 2013. p. 519–26.
164. Lukacz ES, Segall MM, Wexner SD. Evaluation of an Anal Insert Device for the Conservative Management of Fecal Incontinence. Dis Colon Rectum. 2015;58(9):892–8.

165. Segal JP, Leo CA, Hodgkinson JD, Cavazzoni E, Bradshaw E, Lung P, et al. Acceptability, effectiveness and safety of a Renew anal insert in patients who have undergone restorative proctocolectomy with ileal pouch anal anastomosis. Color Dis. 2018;21((1)):73–8.
166. Hotouras A, Ribas Y, Allison M, Murphy J. The CONFIDeNT trial. Lancet [Internet]. 2016;387(10019):643–4. Available from: http://dx.doi.org/10.1016/S0140-6736(16)00281-6
167. Williams AE, Croft J, Napp V, Corrigan N, Brown JM, Hulme C, et al. SaFaRI: sacral nerve stimulation versus the FENIX^{TM} magnetic sphincter augmentation for adult faecal incontinence: a randomised investigation. Int J Colorectal Dis. 2016 Feb 1;31(2):465–72.
168. Gibbs DH, Hooks VH. Overlapping sphincteroplasty for acquired anal incontinence. South Med J. 1993;86(12):1376–80.
169. Paterson HM, Bartolo DCC. Surgery for faecal incontinence. Scott Med J. 2010;55(3):39–42.
170. Jarrett MED, Mowatt G, Glazener CMA, Fraser C, Nicholls RJ, Grant a M, et al. Systematic review of sacral nerve stimulation for faecal incontinence and constipation. Vol. 91, British Journal of Surgery. 2004. p. 1559–69.
171. Thanago E. Neural stimulation for bladder control. Semin Neurol. 1988;170–3.
172. Matzel KE, Stadelmaie U, Gall FP, Hohenfellner M. Electrical stimulation of sacral spinal nerves for treatment of faecal incontinence. Lancet. 1995;346(8983):1124–7.
173. Maeda Y, Lundby L, Buntzen S, Laurberg S. Outcome of sacral nerve stimulation for fecal incontinence at 5 years. Ann Surg. 2014;259((6)):1126–31.

174. Vaizey CJ, Kamm MA, Turner IC, Nicholls RJ, Woloszko J. Effects of short term sacral nerve stimulation on anal and rectal function in patients with anal incontinence. Gut. 1999;44(3):407–12.
175. George A, Nicholls RJ, Vaizey CJ. Long term outcomes of sacral nerve stimulation for faecal incontinence. Gut. 2011;60(Suppl 1):A156–7.
176. Hollingshead JRF, Dudding TC, Vaizey CJ. Sacral nerve stimulation for faecal incontinence: Results from a single centre over a 10-year period. Color Dis [Internet]. 2011;13(9):1030–4. Available from: http://doi.wiley.com/10.1111/j.1463-1318.2010.02383.x
177. Norderval S. Long-term outcomes of sacral nerve stimulation for faecal incontinence (Br J Surg 2015; 102: 407-415). Vol. 102, British Journal of Surgery. 2015. p. 415.
178. Graf W, Mellgren A, Matzel KE, Hull T, Johansson C, Bernstein M. Efficacy of dextranomer in stabilised hyaluronic acid for treatment of faecal incontinence: A randomised, sham-controlled trial. Lancet. 2011;377(9770):997–1003.
179. Danielson J, Karlbom U, Sonesson AC, Wester T, Graf W. Submucosal injection of stabilized nonanimal hyaluronic acid with dextranomer: A new treatment option for fecal incontinence. Dis Colon Rectum. 2009;52((6)):1101–6.
180. Mellgren A, Matzel KE, Pollack J, Hull T, Bernstein M, Graf W, et al. Long-term efficacy of NASHA Dx injection therapy for treatment of fecal incontinence. Neurogastroenterol Motil. 2014;26(8):1087–94.
181. Tjandra JJ, Lim JF, Hiscock R, Rajendra P. Injectable silicone biomaterial for fecal incontinence caused by internal anal sphincter dysfunction is effective. Dis Colon Rectum. 2004;47((12)):2138–46.
182. La Torre M, Lisi G, Milito G, Campanelli M, Clementi I. Sphinkeeper™

for faecal incontinence: a preliminary report. Color Dis. 2019;22((1)):80–5.

183. Litta F, Parello A, De Simone V, Campennì P, Orefice R, Marra AA, et al. Efficacy of Sphinkeeper™ implant in treating faecal incontinence. Br J Surg. 2020;107((5)):484–8.
184. Tan E, Ngo N-T, Darzi A, Shenouda M, Tekkis PP. Meta-analysis: sacral nerve stimulation versus conservative therapy in the treatment of faecal incontinence. Int J Colorectal Dis [Internet]. 2011;26(3):275–94. Available from: http://link.springer.com/10.1007/s00384-010-1119-y
185. Wexner SD, Hull T, Edden Y, Coller JA, Devroede G, McCallum R, et al. Infection rates in a large investigational trial of sacral nerve stimulation for fecal incontinence. J Gastrointest Surg. 2010;14(7):1081–9.
186. Matzel KE, Lux P, Heuer S, Besendörfer M, Zhang W. Sacral nerve stimulation for faecal incontinence: Long-term outcome. Color Dis. 2009;11(6):636–41.
187. Litta F, Parello A, De Simone V, Campennì P, Orefice R, Marra AA, et al. Efficacy of Sphinkeeper™ implant in treating faecal incontinence. Br J Surg. 2020;
188. Devesa JM, Vicente R. The use of a simple anal sling in the management of anal incontinence. Gastroenterol Rep [Internet]. 2014;2(2):136–9. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=prem&NEWS=N&AN=24759346
189. Mellgren A, Wexner SD, Coller JA, Devroede G, Lerew DR, Madoff RD, et al. Long-term efficacy and safety of sacral nerve stimulation for fecal incontinence. Dis Colon Rectum. 2011;54(9):1065–75.
190. Maeda Y, Lundby L, Buntzen S, Laurberg S. Suboptimal outcome

following sacral nerve stimulation for faecal incontinence. Br J Surg. 2011;98(1):140–7.

191. Altomare DF, Binda GA, Dodi G, La Torre F, Romano G, Rinaldi M, et al. Disappointing long-term results of the artificial anal sphincter for faecal incontinence. Br J Surg. 2004;91(10):1352–3.
192. Boyle DJ, Murphy J, Hotouras A, Allison ME, Williams NS, Chan CL. Electrically stimulated gracilis neosphincter for end-stage fecal incontinence: The long-term outcome. Dis Colon Rectum. 2014;57(2):215–22.
193. Matzel KE, Lux P, Heuer S, Besendörfer M, Zhang W. Sacral nerve stimulation for faecal incontinence: Long-term outcome. Color Dis. 2009;11(6):636–41.
194. van der Jagt PKN, Dik P, Froeling M, Kwee TC, Nievelstein RAJ, ten Haken B, et al. Architectural configuration and microstructural properties of the sacral plexus: A diffusion tensor MRI and fiber tractography study. Neuroimage. 2012;62(3):1792–9.
195. Soares JM, Marques P, Alves V, Sousa N. A hitchhiker's guide to diffusion tensor imaging. Front Neurosci. 2013;(7 MAR).
196. Pujol S, Wells W, Pierpaoli C, Brun C, Gee J, Cheng G, et al. The DTI Challenge: Toward Standardized Evaluation of Diffusion Tensor Imaging Tractography for Neurosurgery. J Neuroimaging. 2015;
197. Johansen-Berg H, Behrens TEJ. Just pretty pictures? What diffusion tractography can add in clinical neuroscience. Vol. 19, Current Opinion in Neurology. 2006. p. 379–85.

APPENDIX 1: Ethical statements.

- *'Normative values of Anopress'* has been approved by Modena Research Ethics Committee (Italy), Università degli Studi di Modena e Reggio Emilia, 'Evaluation of normal values using Anopress in healthy subjects', No 247/17;

- *'Initial Evaluation of Anopress in patients with faecal incontinence'* has been approved by the London North West NHS Trust Research & Development Office, 'Ano-rectal physiology: service evaluation of THD Anopress', SE16/039;

- *'Comparing Anopress to the standard water perfused manometry (WPM)'* has been approved by London, Dulwich Research Ethics Committee, the HRA and the London North West NHS Trust Research & Development Office, T'HD Anopress anorectal physiology: comparison of reproducibility of results between water perfused and solid state catheters', 16/LO/1577 and RD16/057;

- *'Initial experience with Renew Anal Insert' has* been approved by the London North West NHS Trust Research & Development Office, 'Renew Anal Insert: an audit for faecal incontinence patients', SUR.St.M.18.001;

- *'Renew VS PTNS: a randomized blinded pilot study'* has been approved by London Harrow Research Ethics Committee, the HRA and the London North West NHS Trust Research & Development Office, 'Randomized pilot study to compare Percutaneous Tibial Nerve Stimulation with the Renew anal plug device for the treatment of the faecal incontinence', 16/LO/1821 and RD16/100; this also obtained a registration in clinicaltrial.gov with the registration number NCT04273009;

- *'Sphinkeeper: first multicentre experience in the UK'* has been approved by the London North West NHS Trust Research & Development Office, 'Sphinkeeper: the new artificial sphincter', SUR.StM.20.030, and by the London Bart's Health NHS Trust, No 7068;

- *'Diffusion Tensor Imaging for assessment of sacral nerve root and computational model of SNS*' has been approved by London Riverside Research Ethics Committee, the HRA and the London North West NHS Trust Research & Development Office, 'Computational model of Sacral Nerve Stimulation (SNS) induced electrical current flow using tractography imaging', 16/LO/1724 and RD16/056;

APPENDIX 2: Study questionnaires.

The CAs online survey: This questionnaire used for the CAs study (Chapter 2.1) was split in 7 main topics.

	DEMOGRAPHICS:
Q1	Your gender is: a- Male b- Female
Q2	Your age is: a- <30 b- 30-50 c- >50
Q3	Address details: City/Town _____ Post Code _____
Q4	What is your background as a continence advisor? Nurse / physiotherapist / other
Q5	How many years have you been a continence advisor? <5 5-10 10-20 >20
Q6	What is the setup of your current practice? a- one worker b- with other therapists c- with GP (same surgery)

Q7	Are you treating: a- Urinary incontinence b- Faecal incontinence c- Both urinary and faecal incontinence
Q8	How many patients in an average month do you see with Urinary Incontinence and how many with Fecal Incontinence? Urinary: <5 5-20 20-50 >50 Faecal: <5 5-20 20-50 >50
	ASSESSMENT
Q9	Do you do: a- Digital examination (PR) (Yes I do / Yes I do and I am feeling confident / No, I do not) b- Diagnose a rectal prolapse (Yes I do / Yes I do and I am feeling confident / No, I do not)
Q10	Do you provide EMG anal sphincter (Yes / No)
	TREATMENT
Q11	Do you prescribe any of the following medications? Loperamide - Co-phenotrope - Colesevelam - Cholestyramine - Probiotics - Charcoal - Aloe vera
Q12	Do you instruct patients to use: a- Suppositories b- Enemas c- Irrigations

Q13	Do you give any dietary advice? a- Low fibre diet b- High fibre diet c- Fodmap diet
Q14	Do you offer any psychological support? Sexual dysfunction b- Body Image c- Anxiety d- Depression
Q15	Do you teach anal pelvic floor exercises /sphincter exercises? (Yes / no)
Q16	Do you teach any urge resistance techniques? (Yes / no)
Q17	Do you provide: a- Electrical stimulation of the anal sphincter b- Percutaneous tibial nerve stimulation (PTNS)
Q18	Do you recommend "Squeezy", the NHS pelvic floor exercise app? (Yes / no)
Q19	Do you recommend Anal Plugs? (Yes / no) If yes, which one: a- Coloplast b- Renew
Q20	Do you provide pads for faecal incontinence? (Yes / no)
Q21	Do you recommend "Shreddies" Pants? (Yes / no)
	FACTORS INFLUENCING TREATMENT CHOICE
Q22	How would you choose a product? (choose one for each category, 1 = least important, 2, 3, 4, 5 = most important, do not know) a- Marketing b- Cost c- Patient's choice / preference d- Practice surgery's choice / preference e- Sponsorship

	TREATMENT FAILURE
Q23	What percentages of your patients are reported on to hospital-based specialists? 0-20 20-40 40-60 60-80 80-100
	EDUCATIONAL SUPPORT
Q24	Do you attend any of the following courses? (Yes / No / Would like to / Unable (funding, time). Choose one for each category) - Courses run by manufacturer - Hospital courses - GP courses - University
Q25	Do you feel you are supported in your daily practice? (Yes / no / not sure)
	FEEDBACK
Q26	Any other comments or suggestions?

Table Anopress values: Here are listed all the values expressed by Anopress. These can be visualised in the main screen and easily interpreted.

- **Anal Cutaneous Reflex:** initial pressure peak that represents the guard anal reflex.
- **Resting pressure:** pressure wave with a steady and constant development, without significant peaks. This is the expression of the pressure of the internal sphincter at rest.
- **Maximum voluntary squeeze:** the highest recorded pressure during the squeeze manoeuvre.
- **Squeeze increment:** the maximum highest recorded pressure minus the main resting pressure. This pressure is also recorded during the squeeze manoeuvre.
- **Endurance (expressed in seconds):** reflecting the length of a voluntary contraction of the external sphincter for the time that it exceed the 50% of the maximum squeeze/maximum rest pressure rate.
- **Cough squeeze (involuntary squeeze):** the maximum squeeze recorded during the cough manoeuvre.
- **Strain pressure:** wave the normally slightly increase at first and then decreases and stabiles to the resting pressure values. This happens during the push manoeuvre which simulates the defecation.
- **(Max/Rest) Maximum pressure/resting pressure rate (expressed in folds):** describes how many times the top squeeze pressure exceed the mean resting pressure.

- **(%Avg/Max) Percentage of Mean resting pressure/mean strain pressure:** reflects the percentage of increase or reduction of pressure during the whole phase of strain, compared to the mean resting pressure.

- **(%Avg/Rest Avg) The mean strain/mean resting percentage rate:** it is the comparison between the pressure at rest and the pressure during the attempted defecation phase. The negativity of the percentage is seen in normal individuals, when the pressure during strain is lower than during the rest phase, expressing a relaxation of the muscular complex. A positive percentage, especially above 20%, can be seen in individuals with paradoxical contraction of the external sphincter during defecation, and is common in patients complaining with obstructed defecation syndrome.

St Mark's questionnaire: The St Mark's faecal incontinence score used to assess the severity of incontinence symptoms, Vaizey et al., St Mark's Hospital (57).

Type of incontinence	Frequency				
	Never	**Rarely**	**Sometimes**	**Usually**	**Always**
Solid	0	1	2	3	4
Liquid	0	1	2	3	4
Gas	0	1	2	3	4
Lifestyle alteration	0	1	2	3	4
				No	Yes
Need to wear a pad or plug				0	2
Taking constipating medicines				0	2
Lack of ability to defer defecation for 15 minutes				0	4

Never = no episodes in the past four weeks; Rarely = 1 episode in the past four weeks;

Sometimes = >1 episode in the past four weeks but <1 a week; Usually = 1 or more episodes a week but <1 a day; Always = 1 or more episodes a day.

Add one score from each row.

Minimum score is 0 = perfect continence; maximum score is 24 = totally incontinent.

Two weeks bowel diary: This diary was used as for standard care to collect patient's daily bowel habit. Patients normally should fill this diary for 14 consecutive days.

Day	Time	Urgency Rating	Did you leak or loose bowel content? (Y/N)	If yes, please indicate amount of uncontrolled leakage or loss of bowel content	Comments
1					
2					
…					

ICQ-B questionnaire: This quality of life score was used for the randomised controlled trial (Section 4.2.2) – from next page -.

Initial number

ICIQ-B (04/08)

CONFIDENTIAL

DAY MONTH YEAR

Today's date

Many people experience bowel accidents or bowel leakages. We are trying to find out how many people experience these symptoms and how much this bothers them. We would be grateful if you could answer the following questions, thinking about how you have been over the PAST THREE MONTHS.

1 Please write in your date of birth:

DAY MONTH YEAR

2 Are you *(tick one)*: Female ☐ Male ☐

Bowel pattern

3 On average how many times do you open your bowels in 24 hours?
(Tick one box for 'usual' and tick one box for 'at worst')

	(a) Usual	(b) At worst
less than once	☐ 1	☐ 1
one to three times	☐ 2	☐ 2
three to ten times	☐ 3	☐ 3
ten or more times	☐ 4	☐ 4

(c) **How much does this bother you?**
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

4 How often do you open your bowels during the night from going to bed to sleep until you get up in the morning? *(Tick one box)*

	(a)
never	☐ 0
once	☐ 1
twice	☐ 2
three times	☐ 3
four or more times	☐ 4

(b) **How much does this bother you?**
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

Bowel control

8 **Do you experience any staining of your underwear or need to wear pads because of your bowels?** *(Tick one box)*

(a)

never ☐ 0
less than once a month ☐ 1
less than once a week ☐ 2
less than once a day ☐ 3
everyday ☐ 4

(b) **How much does this bother you?**
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

9 **Are you able to control watery or loose stool leaking from your back passage?** *(Tick one box)*

(a)

always ☐ 0
most of the time ☐ 1
some of the time ☐ 2
rarely ☐ 3
never ☐ 4

(b) **How much does this bother you?**
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

10 **Are you able to control accidental loss of formed or solid stool from your back passage?** *(Tick one box)*

(a)

always ☐ 0
most of the time ☐ 1
some of the time ☐ 2
rarely ☐ 3
never ☐ 4

(b) **How much does this bother you?**
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

11 **Are you able to control wind (flatus) escaping from your back passage?**
(Tick one box)

(a)

always	0
most of the time	1
some of the time	2
rarely	3
never	4

(b) **How much does this bother you?**
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

12 **Are you able to control mucus (discharge) leaking from your back passage?**
(Tick one box)

(a)

always	0
most of the time	1
some of the time	2
rarely	3
never	4

(b) **How much does this bother you?**
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

13 **Do you have bowel accidents when you have no need to open your bowels?**
(Tick one box)

(a)

never	0
rarely	1
some of the time	2
most of the time	3
always	4

(b) **How much does this bother you?**
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

14 **Are your bowel accidents or leakages <u>unpredictable</u>?** *(Tick one box)*

(a)

never ☐ 0
rarely ☐ 1
some of the time ☐ 2
most of the time ☐ 3
always ☐ 4

(b) **How much does this bother you?**
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

Bowel control score: sum scores 8a – 14a ☐☐

Other bowel symptoms

15 **Using the pictures please indicate how your bowel movements are <u>most</u> of the time?** *(Tick all boxes that apply)*

(a)

separate hard lumps like nuts (hard to pass)  ☐ 1
sausage-shaped but lumpy  ☐ 2
like a sausage but with cracks on its surface  ☐ 3
like a sausage or snake – smooth and soft  ☐ 4
soft blobs with clear cut edges (easy to pass)  ☐ 5
fluffy pieces with ragged edges, a mushy stool  ☐ 6
watery, no solid pieces  ☐ 7

(b) **How much does this bother you?**
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

16 **Do you need to strain to open your bowels?** *(Tick one box)*

(a)

never ☐ 0
rarely ☐ 1
some of the time ☐ 2
most of the time ☐ 3
always ☐ 4

(b) **How much does this bother you?**
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

17 **Is the possibility of having a bowel accident on your mind?** *(Tick one box)*

(a)

never ☐ 0
rarely ☐ 1
some of the time ☐ 2
most of the time ☐ 3
always ☐ 4

(b) **How much does this bother you?**
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

Sexual impact

18 **Do you restrict your sexual activities because of your bowels?** *(Tick one box)*

(a)

never ☐ 0
rarely ☐ 1
some of the time ☐ 2
most of the time ☐ 3
always ☐ 4
not applicable ☐ 5

(b) **How much does this bother you?**
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal