Studies of diagnostic and surgical modalities in refractory constipation

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Submitted in partial fulfillment of the requirements of the degree of Doctor of Philosophy

i. STATEMENT OF ORIGINALITY

I, UGO GROSSI, confirm that the research included within this thesis is my own work or that where it has been carried out in collaboration with, or supported by others, that this is duly acknowledged below and my contribution indicated. Previously published material is also acknowledged below.

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ii. PEER REVIEW PUBLICATIONS AND PRIZES ASSOCIATED WITH THIS THESIS

1. Grossi U, Di Tanna GL, Heinrich H, Taylor SA, Knowles CH, Scott SM. Letter: limitations of defaecography among patients with refractory constipation. Authors' reply. Aliment Pharmacol Ther. 2019 Jul;50(1):112-113. doi: 10.1111/apt.15309.

2. Grossi U, Di Tanna GL, Heinrich H, Taylor SA, Knowles CH, Scott SM. Systematic review and meta-analysis: defaecography should be a first-line diagnostic modality in patients with refractory constipation. Aliment Pharmacol Ther. 2018 Dec;48(11-12):1186-1201. doi: 10.1111/apt.15039.

3. Grossi U, Stevens N, McAlees E, Lacy-Colson J, Brown S, Dixon A, Di Tanna GL, Scott SM, Norton C, Marlin N, Mason J, Knowles CH. Stepped-wedge randomised trial of laparoscopic ventral mesh rectopexy in adults with chronic constipation: study protocol for a randomized controlled trial. Trials. 2018 Feb 5;19(1):90. doi: 10.1186/s13063-018-2456-3.

4. Knowles CH, Grossi U, Horrocks EJ, Pares D, Vollebregt PF, Chapman M, Brown SR, Mercer-Jones M, Williams AB, Hooper RJ, Stevens N, Mason J, on behalf of the NIHR CapaCiTY working group and The Pelvic Floor Society. Surgery for constipation: systematic review and clinical guidance. Paper 1: introduction & methods. Colorectal Dis. 2017 Sep;19 Suppl 3:5-16. doi: 10.1111/codi.13774. Review.

5. Knowles CH, Grossi U, Chapman M, Mason J, on behalf of the NIHR CapaCiTY working group and Pelvic Floor Society. Surgery for constipation: systematic review and practice recommendations. Results I: colonic resection. Colorectal Dis. 2017 Sep;19 Suppl 3:17-36. doi: 10.1111/codi.13779. Review.

6. Grossi U, Knowles CH, Mason J, Lacy-Colson J, Brown SR, on behalf of the NIHR CapaCiTY working group and Pelvic Floor Society. Surgery for constipation: systematic review and practice recommendations. Results II: hitching procedures for the rectum (rectal suspension). Colorectal Dis. 2017 Sep;19 Suppl 3:37-48. doi: 10.1111/codi.13773. Review.

7. Mercer-Jones M, Grossi U, Pares D, Vollebregt PF, Mason J, Knowles CH, on behalf of the NIHR CapaCiTY working group and Pelvic Floor Society. Surgery for constipation: systematic review and practice recommendations. Results III: rectal wall excisional procedures (rectal excision). Colorectal Dis. 2017 Sep;19 Suppl 3:49-72. doi: 10.1111/codi.13772. Review.

8. Grossi U, Horrocks EJ, Mason J, Knowles CH, Williams AB, on behalf of the NIHR CapaCiTY working group and Pelvic Floor Society. Surgery for constipation: systematic review and practice recommendations. Results IV: recto-vaginal reinforcement procedures. Colorectal Dis. 2017 Sep;19 Suppl 3:73-91. doi: 10.1111/codi.13781. Review.

9. Knowles CH, Grossi U, Horrocks EJ, Pares D, Vollebregt PF, Chapman M, Brown SR,

Mercer-Jones M, Williams AB, Hooper RJ, Stevens N, Mason J, on behalf of the NIHR CapaCiTY working group and The Pelvic Floor Society and European Society of Coloproctology. Surgery for constipation: systematic review and practice recommendations. Graded practice and future research recommendations. Colorectal Dis. 2017 Sep;19 Suppl 3:101-113. doi: 10.1111/codi.13775. Review.

10. Parés D, Drami I, Adams K, Grossi U, Suliman I, Knowles CH. Use of the harmonic scalpel for Delorme's procedure. Colorectal Dis. 2017 Apr 18.

11. Norton C, Emmanuel A, Stevens N, Scott SM, Grossi U, Bannister S, Eldridge S, Mason JM, Knowles CH. Habit training versus habit training with direct visual biofeedback in adults with chronic constipation: study protocol for a randomised controlled trial. Trials. 2017 Mar 24;18(1):139.

12. Grossi U, Carrington EV, Bharucha AE, Horrocks E, Scott SM, Knowles CH. Diagnostic accuracy study of anorectal manometry for diagnosis of dyssynergic defaecation. Gut. 2016 Mar;65(3):447-55. doi: 10.1136/gutjnl-2014-308835. Epub 2015 Mar 12.

13. Carrington EV, Grossi U, Knowles CH, Scott SM. Normal values for high-resolution anorectal manometry: a time for consensus and collaboration. Neurogastroenterol Motil. 2014 Sep;26(9):1356-7. doi: 10.1111/nmo.12364.

ii.i PEER REVIEWED ABSTRACTS FOR PRESENTATION AT LEARNED SOCIETIES

1. Grossi U, Di Tanna GL, Heinrich H, Taylor SA, Knowles CH, Scott SM. Defaecography: first-line diagnostic modality in patients with refractory constipation? Implications from a systematic review and meta-analysis. The First UK Pelvic Floor Summit, Telford, 18/04 – 20/04/2018 (oral presentation).

2. Grossi U, Knowles CH, Hooper R, Newman P, Thomas L, Dixon AR. Outcome of laparoscopic ventral mesh rectopexy for internal rectal prolapse: a retrospective cohort study of 546 patients with independent data analysis. 7th Meeting of the Italian Society of Colorectal Surgery, Rome, 30/09 – 03/10/2017 (oral presentation).

3. Grossi U, Hooper R, Newman PA, Thomas L, Dixon AR, Knowles CH. Outcome of laparoscopic ventral mesh rectopexy for internal rectal prolapse: a prospective cohort study of 546 patients with independent data analysis. 12th Scientific and Annual Meeting of the European Society of Coloproctology, Berlin (Germany), 20-22/09/2017 (oral presentation).

4. Carrington EV, Grossi U, Knowles CH, Scott SM. 'Pelvic floor akinesia' - a highly specific manometric finding in patients with defaecatory dysfunction. Digestive Disease Week, Chicago (IL), USA, 06-09/05/2017 (oral presentation).

5. Grossi U, Carrington EV, Knowles CH, Scott SM. Diagnostic accuracy study of anorectal manometry for diagnosis of dyssynergic defaecation. 1st Federation Neurogastroenterology and Motility Scientific Meeting, 5-7/09/2014, Guangzhou, China (poster presentation).

ii.ii PRIZES

2014	Poster of distinction Federation of Neurogastroenterology and Motility.
2016	Ettore Ruggieri prize Italian Society of Surgery
2017	John Nicholls prize Italian Society of Colorectal Surgery

iii. ABSTRACT

i) The aims were to:

1. Explore the diagnostic accuracy of anorectal manometry (AM) for diagnosis of dyssynergic defaecation;
2. Examine the yield of defaecography in patients with chronic constipation (CC) and healthy volunteers (HV) through systematic review and meta-analysis;
3. Examine the prevalence of defaecographic structural and functional abnormalities in a single-centre series of consecutive CC sufferers;
4. Explore outcomes of laparoscopic ventral mesh rectopexy (LVMR) for symptomatic intussusception;
5. Contribute to protocol development for a stepped-wedge randomized controlled trial of LVMR for intussusception.

ii) Methods

Epidemiological studies were conducted:

1. A diagnostic accuracy study of high-resolution AM to detect dyssynergic patterns of defaecation in HV and CC;
2. A systematic review and meta-analysis of studies reporting prevalence, definitions and cut-offs of defaecographic abnormalities in CC;
3. A cross-sectional study exploring the prevalence of defaecographic abnormalities in CC;
4. A systematic review and meta-analysis of studies reporting outcomes of hitching procedures (rectal suspension) for refractory constipation;
5. A large retrospective cohort study of patients undergoing LVMR for internal rectal prolapse (IRP);
6. The protocol for a randomized controlled trial (CapaCiTY 3) of LVMR for IRP was also developed.

iii) Results

1. Only 9% of all participants exhibited the accepted ‘normal’ pattern of rectoanal coordination. A total of 94% of CC patients and 87% of HV had abnormal manometric patterns during simulated defaecation; some individual patterns discriminated CC from HV, e.g. the type IV pattern was modestly useful (i.e., PPV 70%, LR+ 2.3).

2. Multiple structural and functional defaecographic abnormalities may coexist in the same subject, with degree of overlap greater than previously recognized. The principal phenotypes encountered were normal defaecography (16%) and isolated functional abnormalities (13%), both significantly more prevalent in males than females. Coexistence of structural abnormalities was significantly more often encountered in females, reflecting global pelvic floor weakness.

3. A systematic review of evidence for the perioperative and long terms benefits and harms of rectal suspension procedures identified no high quality studies. The evidence base is characterised by observational studies of variable and often uncertain methodological quality. Definitions are poor, e.g. grading of complications was inconsistent.

4. Older age and previous urogenital prolapse surgery were independently associated with poorer quality of life at 12 months after LVMR. Mesh type was associated with mesh complication-free survival (p=0.001): polypropylene and titanium-coated lightweight polypropylene (TCLP) had better survival than polyester (HR 0.25 [95%CI0.11-0.54], 0.31 [95%CI0.09-1.06], respectively). Mesh type was strongly predictive of time to recurrence of prolapse (p<0.001), with polypropylene having the best recurrence-free survival, and TCLP the worst (HR 0.07 [95%CI0.02-0.34] vs. 2.93 [95%CI1.31-6.55], respectively). SRUS was independently associated with earlier recurrence of prolapse (HR 2.95, 95%CI1.05-8.27).

iv) Conclusions

1. AM ‘push’ manoeuvre has limited utility for distinguishing between constipated and healthy subjects.

2. Pathologically significant structural abnormalities, as well as functional abnormalities, are common in CC patients. Since structural abnormalities cannot be evaluated using non-imaging test modalities (balloon expulsion and AM), defaecography should be considered first-line diagnostic test, if resources allow.

3. LVMR is clinically effective in the medium term for symptomatic relief of IRP. Choice of mesh strongly influences mesh complications and recurrence. CapaCiTY 3 might confirm (or refute) these findings.

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vii. ACKNOWLEDGEMENTS

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FOR Carla

viii. LIST OF ABBREVIATIONS

3DED	3-D echodefaecography
ACPGBI	Association of Coloproctology of Great Britain and Ireland
AM	anorectal manometry
BBUSQ	Birmingham Bowel and Urinary Symptoms Questionnaire
BD	barium X-ray defaecography
BET	balloon expulsion test
BIPQ-CC	Brief Illness Perception Questionnaire-Chronic Constipation
CapaCiTY	Chronic Constipation Treatment PathwaY
CC	chronic constipation
CC-BRQ	Chronic Constipation-Behavioural Response to illness Questionnaire
CCCS	Cleveland Clinic Constipation score
CCIS	Cleveland Clinic incontinence score
CRAG	constipation research advisory group
ED	evacuation disorder
ERP	external rectal prolapse
DDV	defaecatory desire volume
DMEC	data monitoring & ethics committee
DOMACLES	DAta MOnitoring Committees: Lessons, Ethics, Statistics
DTPU	dynamic transperineal ultrasonography
FAR	failed anal relaxation
FDD	functional defaecation disorder

FI	faecal incontinence
FIQL	Faecal Incontinence Quality of Life
FISI	Faecal Incontinence Severity Index
GAD7	Generalized Anxiety Disorder7
GIQLI	Gastrointestinal Quality of Life Index
GSR	global satisfaction ratings
HRAM	high-resolution anorectal manometry
HV	healthy volunteers
INVEST	radio-physiological investigations
IRP	internal rectal prolapse
LVMR	laparoscopic ventral mesh rectopexy
MDT	multidisciplinary decision team
MRID	magnetic resonance imaging defaecography
MSHQ-EjD	Male Sexual Health Questionnaire-Ejaculatory Dysfunction
NHS	National Health Service
NICE	National Institute of Clinical Excellence
NIHR	National Institute for Health Research
ODS	obstructive defaecation score
PAC-QOL	Patient Assessment of Constipation-Quality of Life
PAC-SYM	Patient Assessment of Constipation-Symptoms
PARA	posterior anorectal angle
PCS	prospective case series
PE	polyester
PHQ-9	Patient Health Questionnaire-9

PISQ-12	Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire-12
PP	polypropylene
PPI	patient and public involvement
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSC	programme steering committee
QALY	quality adjusted life year
QOL	quality of life
RAPG	rectoanal pressure gradient
RCH	retrospective cohort study
RCS	retrospective case series
RCT	randomised controlled trial
ROC	receiver operating characteristic
SF-36	Short Form-36
SMIS	St Marks Incontinence score
SPIRIT	Standard Protocol Items: Recommendations For Interventional Trials
SRUS	solitary rectal ulcer syndrome
STARD	Standards for Reporting Diagnostic Accuracy
TCLP	titanium-coated lightweight polypropylene
UK	United Kingdom
US	United States

Chapter 1 - Introduction

1.1. Definition, epidemiology and economic burden of constipation

Constipation is a syndrome characterized by symptoms of unsatisfactory defaecation associated with infrequent stools and/or difficult stool passage. The latter include straining, a sense of difficulty passing stool, incomplete evacuation, hard/lumpy stools, prolonged time to stool, or need for manual manoeuvres to aid faecal expulsion (American College of Gastroenterology Chronic Constipation Task 2005).

The term "constipation" comes from French medical literature of the 17th century (Dubé 1686). Etymologically, it origins from Latin *cum* "together" and *stipare* "to cram", which, in turn, comes from Greek *στύφω* \ *stýpho* \ "to bind hard". A basic pathophysiological mechanism of constipation can be found in an Egyptian pharmaceutical papyrus from the 16th century BC (the oldest complete medical text in existence) (http://sae.saw-leipzig.de/detail/dokument/papyrus-ebers/), as the notion that the body is poisoned by material released from decomposing waste in the intestines (Benninga and Scott 2011).

Constipation is common in adults and children and affects 14-15% of the population depending on definitions used (2-28% adults; 0.7-30% children), with a higher prevalence in women (Sonnenberg and Koch 1989, McCrea et al. 2009, Mugie et al. 2011, Suares and Ford 2011) and the elderly (Norton 2006, Gallegos-Orozco et al. 2012).

Constipation can be acute (typically <1-week duration) or chronic (>3 months, in accordance with consensus criteria) (Camilleri et al. 2017). Chronic constipation (CC) is less common (Probert et al. 1995), with a pooled prevalence in the community of 14%

and significant cost and healthcare use resulting in 0.5 million consultations per annum with general practitioners in United Kingdom (UK) (Suares and Ford 2011). Approximately 1-2% of the population suffer symptoms that are both chronic and more disabling (Cook et al. 2009). Such patients, who are very frequently female (Knowles et al. 2003), are usually referred to secondary care with many progressing to tertiary specialist investigation. Patient dissatisfaction is high in this group: nearly 80% feel that laxative therapy is unsatisfactory (Wald et al. 2008) and the effect of symptoms on measured quality of life (QOL) is significant (Irvine et al. 2002). CC consumes significant healthcare resources: in the United States (US) in 2012, a primary complaint of constipation was responsible for 3.2 million physician visits (Peery et al. 2012) resulting in (direct and indirect) costs of $1.7 billion. In the UK, it is estimated 10% of district nursing time is spent on constipation (Poulton and Thomas 1999) and the annual spend on laxatives exceeds £80 million, with £17.4 million prescriptions in 2012 (Health and Social Care Information Centre, 2013) (Centre 2013).

1.2. Pathophysiological basis of chronic constipation

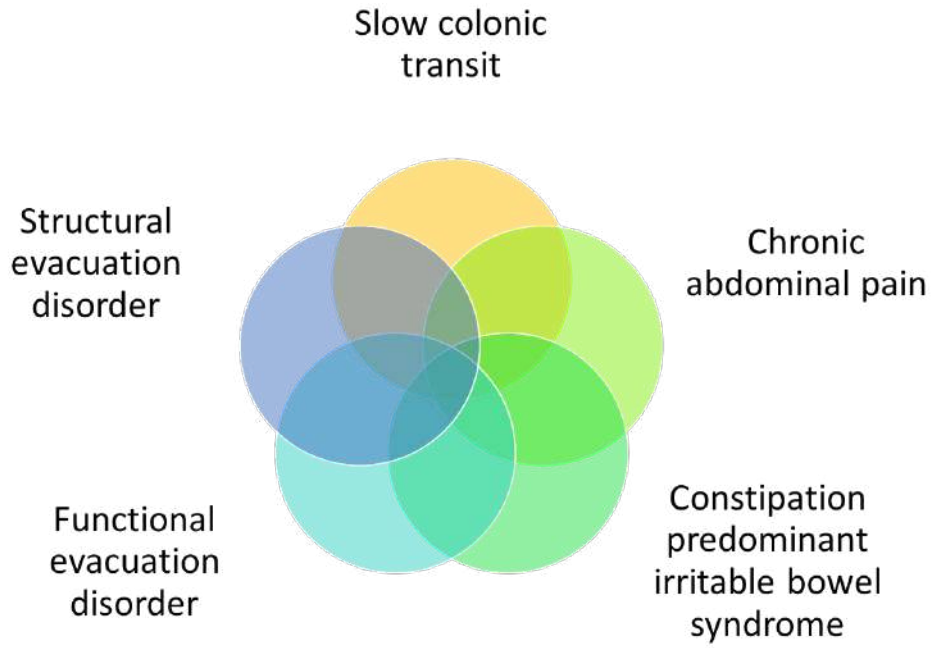
The act of defaecation is dependent on the coordinated functions of the colon, rectum and anus. Considering the complexity of neuromuscular (sensory and motor) functions required to achieve planned, conscious, and effective defaecation (Scott et al. 2011), it is no surprise that disturbances to perceived 'normal' function occur commonly at all stages of life. Clinically, such problems often lead to symptoms of obstructed defaecation (e.g. straining; incomplete, unsuccessful or painful evacuation; bowel infrequency; abdominal pain and bloating). After exclusion of a multitude of secondary causes, the pathophysiology of CC can broadly be divided into problems of colonic

contractile activity, and thus stool transit, and sensorimotor and anatomical problems of the anorectum and pelvic floor leading to evacuatory difficulty. Thus, with specialist radio-physiological investigations, patients may be divided into those who have slow colonic transit, an evacuation disorder (ED), both or neither (no abnormality found with current tests) (Table 1.1).

TABLE 1.1 - CAUSES OF CHRONIC CONSTIPATION.

Chronic constipation

Primary constipation



Secondary constipation

- Medications: opioids, Ca^{2+} blockers, α2-adrenergic agonists, tricyclic antidepressants, 5-hydroxytryptamine receptor 3 antagonists, dopaminergic drugs, anticholinergic drugs, neuroleptics and chemotherapeutic agents.
- Disorders of electrolyte balance: hypercalcaemia and hypokalaemia.
- Hormonal changes: hypothyroidism and pregnancy.
- Psychiatric disorders: depression and eating disorders.
- Neurological disorders: Parkinson disease, multiple sclerosis and spinal cord injury.
- Ageing: immobility and comorbid conditions.
- Generalized muscle disease: progressive systemic sclerosis and amyloidosis.
- Organic disease of the gastrointestinal tract: colorectal cancer or polyps.

EDs can be then sub-classified into those in which a structurally significant pelvic floor abnormality is evident (e.g. large rectocoele or high-grade internal prolapse

[intussusception]), and those in which there is a dynamic failure of evacuation without structural abnormality, most commonly termed 'functional defaecation disorder (FDD)'. This group of patients are unable to achieve coordination of abdominal, rectal, anal and pelvic floor muscles during attempted defaecation (Rao et al. 1998). This manifests as paradoxical anal contraction, inadequate anal relaxation, sensory disturbance and/or impaired rectal propulsive force (Mahieu et al. 1984, Townsend et al. 2016).

1.3. Clinical diagnosis of chronic constipation

A detailed medical, surgical, dietary and drug history helps the recognition of CC. Of note, patients' and physicians' perspective of symptoms of CC may differ (Herz et al. 1996) (Dimidi et al. 2019). Therefore, diagnostic criteria have been proposed by experts consensus. Beside the above mentioned ACG definition (American College of Gastroenterology Chronic Constipation Task 2005), the Rome Foundation released the new Rome IV criteria for functional constipation in 2016 (Table 1.2). According to Rome IV, CC forms part of functional bowel disorders in which symptoms of difficult, infrequent, or incomplete defaecation predominate. Patients should not meet IBS criteria, although abdominal pain and/or bloating may be present but are not predominant symptoms. This supports the concept that CC and IBS-C are disorders that exist on a continuous spectrum (Mearin et al. 2016). Symptom onset should occur at least 6 months before diagnosis, and symptoms should be present during the last 3 months.

TABLE 1.2 - ROME IV CRITERIA FOR FUNCTIONAL CONSTIPATION (MEARIN ET AL. 2016).

Diagnostic Criteria^

1. Must include 2 or more of the following:*
   a. Straining during more than one-fourth (25%) of defaecations;
   b. Lumpy or hard stools (Bristol Stool Form Scale 1-2) more than one-fourth (25%) of defaecations;
   c. Sensation of incomplete evacuation more than one-fourth (25%) of defaecations;
   d. Sensation of anorectal obstruction/blockage more than one-fourth (25%) of defaecations;
   e. Manual manoeuvres to facilitate more than one fourth (25%) of defaecations (e.g., digital evacuation, support of the pelvic floor);
   f. Fewer than 3 spontaneous bowel movements per week.
2. Loose stools are rarely present without the use of laxatives.
3. Insufficient criteria for irritable bowel syndrome.

^ *Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.*

* *For research studies, patients meeting criteria for opioid-induced constipation should not be given a diagnosis of functional constipation because it is difficult to distinguish between opioid side effects and other causes of constipation. However, clinicians recognize that these 2 conditions might overlap.*

Inquiring about routine bowel habit (with/without laxatives) and stool consistency (e.g. using the Bristol Stool Scale Form (Lewis and Heaton 1997)), onset (e.g. since childhood) and type of symptoms (e.g. sense of incomplete evacuation or digital assistance to aid faecal expulsion), and perception of an urge to defaecate well fit into the patients' framework (Rao and Meduri 2011). Furthermore, it is important to gently elicit any history of sexual or physical abuse, which were encountered in up to 48% and 74% of constipated patients (Rao et al. 2004). Of note, faecal incontinence and constipation

frequently coexist and incontinence may be a presenting feature of constipation in the elderly secondary to stool impaction (Leung and Rao 2009).

The presence of red flag signs and symptoms (e.g. rectal bleeding, anaemia, abdominal mass) should prompt an enquiry to exclude organic illness and neoplastic disease.

A comprehensive physical examination including neurological assessment is important to recognize secondary causes of constipation. Inspection of the perianal region may reveal abnormalities such as thrombosed external haemorrhoids, skin tags, rectal prolapse, anal fissure, anal warts, excoriation or evidence faecal seepage. Digital rectal examination is of crucial importance to determine the presence of polyps or endoluminal masses, a large rectocoele or significant intussusception. The patient should be asked to push and bear down as if to defaecate. Physiologically, the anal sphincters and puborectalis muscle relax allowing perineal descent. Paradoxical contraction or absent perineal descent may suggest dyssynergic defaecation.

1.3.1 Symptoms scores

Symptoms associated with CC are nonspecific and include straining, hard/lumpy stools, a sense of incomplete evacuation after a bowel movement, a feeling of anorectal blockage, the need for digital assistance or infrequent defaecation (Mearin et al. 2016). Between 1996 and 2008, 5 scoring systems have been developed to assess the severity of CC thus allowing a more accurate evaluation of treatment outcomes:

- The chronic idiopathic constipation index (CICI) (Altomare et al. 1996), was designed to detect chronic idiopathic slow transit constipation using 7 variables (each scored from 0 to 3, with a maximum score of 21). The CICI was the first

questionnaire incorporating features of autonomic neuropathy but has been seldom used in clinical practice;

- The Cleveland Clinic Constipation Score, published in the same year (Agachan et al. 1996), has become quickly popular and internationally accepted. It consists of 8 items (7 of which scored from 0 to 4 and 1 from 0 to 2), for a maximum score of 30;
- The Patient Assessment of Constipation-Symptoms (PAC-SYM) (Frank et al. 1999) incorporates 12 items addressing the patient perspective on the disorder. Only recently, a cut-off of –0.75 has been suggested as "minimal important difference" (e.g. the smallest difference in score that informed patients or proxies perceive as important, and leads the patient or clinician to consider a change in the management) (Yiannakou et al. 2017);
- In 2000, a new, prospectively validated instrument, the Knowles-Eccersley-Scott Symptom (KESS) score, was introduced (Knowles et al. 2000), consisting of 11 items scored from 0 to 3 or 4, for a maximum of 39 points;
- More recently, a 78-item questionnaire, the Constipation Severity Instrument (CSI), was developed to characterize different subtypes of CC (Varma et al. 2008);
- In the same year, the obstructed defaecation syndrome (ODS) score was introduced to specifically assess the severity of ED (Altomare et al. 2008). It consists of 7 items scored from 0 to 4 and 1 item from 0 to 3 with a maximum score of 31.

1.4. Instrumental diagnosis of chronic constipation

In clinical practice, the need to determine the exact clinical phenotype of CC is not often deemed essential if patients are responsive to first-line conservative treatment such as lifestyle advice and laxatives (Camilleri et al. 2017). However, the recognition of individual subtypes may allow tailored treatment, especially in case of failure of primary care, and certainly in patients considered for surgery. Given a considerable symptom overlap within the various subtypes of constipation, this is nowadays achieved with specialist radiophysiological testing often performed in tertiary care centres, and mainly consisting of a variable combination of whole gut transit study, anorectal manometry (AM), electromyography (EMG), balloon expulsion test (BET), and dynamic imaging modalities (defaecography and ultrasonography).

1.4.1. Whole gut or colonic transit study

Intestinal transit time has been measured using 3 general methods: a) ingestion of radio-opaque markers followed by performing plain abdominal x-rays taken at variable times, which generally evaluate whole gut transit; b) by using radioisotope scintigraphy (Camilleri and Zinsmeister 1992, McLean et al. 1999); or c) by wireless motility capsule, where colon transit time is measured from the time the capsule enters the cecum, determined by a sudden drop in pH, to the time it passes out of the colon, determined by a sudden drop in temperature accompanied by a loss of pressure recording (Zarate et al. 2010).

Compared to scintigraphic studies and the wireless motility capsule, the radio-opaque marker technique is cheaper and more widely used in current clinical practice for the

diagnosis of slow transit constipation. Since its first description (Hinton et al. 1969), several methods have been published, differing in the number of markers ingested, number of days on which they are ingested, and number and intervals of abdominal X-rays (Metcalf et al. 1987, Bouchoucha et al. 1992).

The Motilis 3D-Transit system (Motilis Medica SA, Lausanne, Switzerland) is a new ingestible capsule system that allows recordings to be performed at home under near normal physiologic conditions. Compared to the wireless motility capsule, the 3D-Transit system records the 3D position and rotation of up to 3 ingested electromagnetic capsules thus providing detailed information about gut motility. For this reason, it holds promise for future assessment of movement patterns to distinguish between different diseases and effects of treatment (Mark et al. 2019).

1.4.2. Anorectal manometry

Anorectal manometry can record mechanical activity of the anorectum through measurement of changes in intraluminal pressure (Duthie and Watts 1965, Phillips and Edwards 1965) and is now the most established and commonly performed investigation of anorectal function (Rao et al. 2004). Several expert reviews provide guidance on technical performance and interpretation of AM (Rao et al. 2002, Scott and Gladman 2008).

Examination of recto-anal pressure gradient (RAPG) during the bearing down manoeuvre allows assessment of voluntary control of the pelvic floor. It is generally accepted that for defaecation to be successful, RAPG should become positive (i.e. intra-rectal pressures sufficiently exceeding anal pressures) to allow faecal expulsion (Rao et al. 1999). Alteration in the RAPG during simulated evacuation has been observed in

patients with symptoms of ED (Rao et al. 1998, Rao et al. 2004) and has represented the key feature for diagnosing FDD according to the previous Rome (III) criteria (Rao et al. 1999, Bharucha et al. 2006, Bharucha et al. 2006). Four abnormal manometric patterns have been defined (Rao 2008), characterised by a paradoxical increase in anal pressure with (type I) or without (type II) adequate increase in rectal pressure, and failure of reduction in anal pressure with (type III) or without (type IV) adequate increase in rectal pressure (Figure 1.1).

With the advent of high-resolution systems (Carrington et al. 2014), the ability of manometry to distinguish healthy asymptomatic individuals from those with defaecatory symptoms has been questioned (Noelting et al. 2012) because, contrary to conventional wisdom, the RAPG during simulated evacuation was found to be negative in a majority of asymptomatic women (Ratuapli et al. 2013).

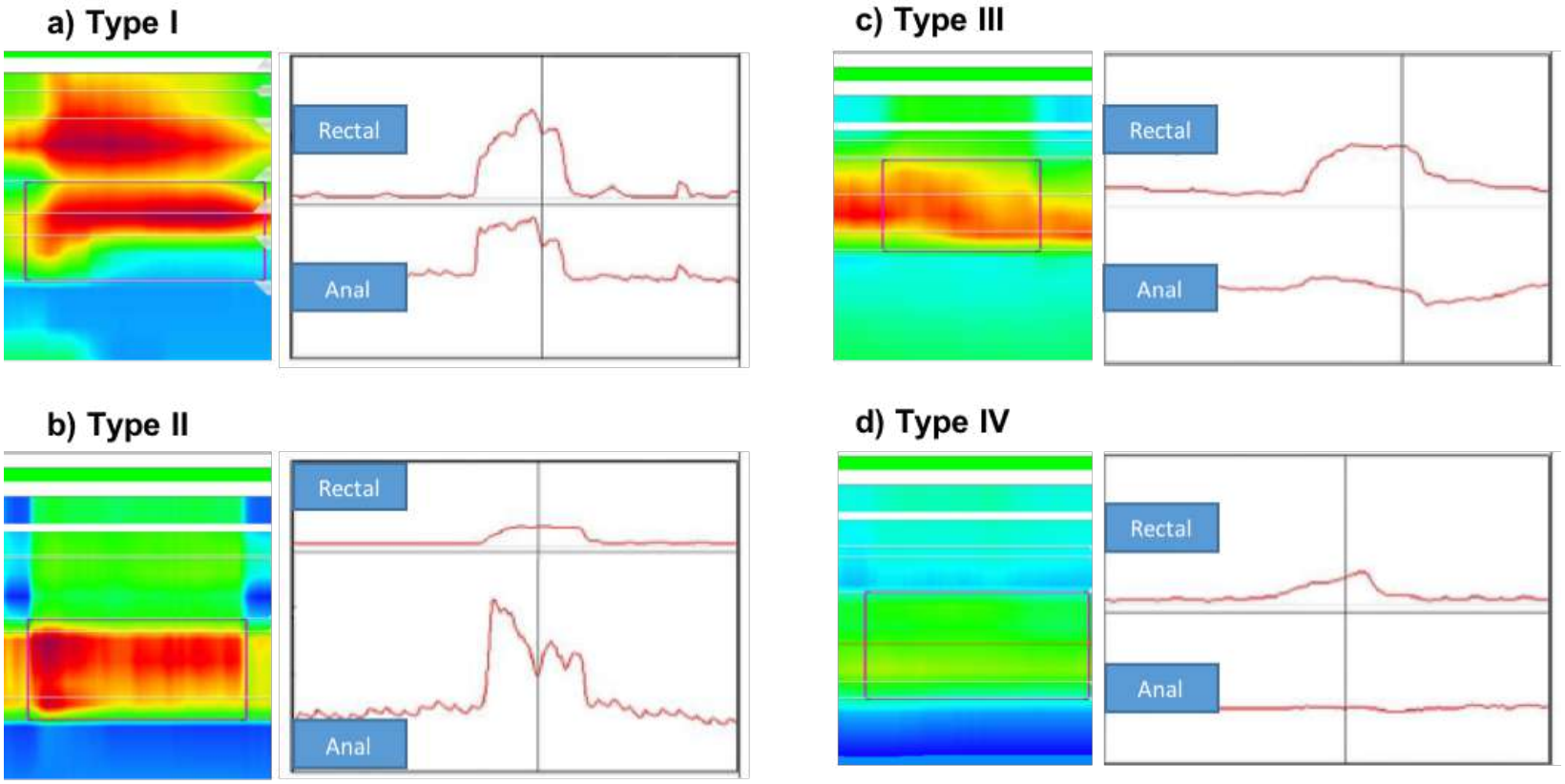


FIGURE 1.1 - ANORECTAL MANOMETRY PATTERNS DURING ATTEMPTED DEFAECATION. HIGH-RESOLUTION ANORECTAL MANOMETRY (COLOUR-CONTOUR PLOTS) AND CONVENTIONAL MANOMETRY (LINE PLOTS) IN THE RECTUM (TOP PANELS) AND ANUS (LOWER PANELS) ARE SHOWN

1.4.3. Electromyography

In 1953, Floyd and Walls described electromyography (EMG) using a surface electrode placed on the skin of the anus (Floyd and Walls 1953). EMG can evaluate pelvic floor musculature by measuring the motor unit action potentials of the muscles (Lefaucheur 2006). Compared to rest, activity of the external anal sphincter normally increases during voluntary contraction and decreases during straining (Porter 1962). EMG studies can identify a failure of the striated puborectalis muscle and the external anal sphincter to relax in some patients with ED (Fucini et al. 2001).

Three main methods of performing EMG have been described: needle or wire (invasive EMG), skin electrode (surface EMG), or anal plugs. Equivalence of the first 2 methods has been shown (Axelson and Edebol Eeg-Olofsson 2010), with surface EMG carrying 91% negative predictive value to rule out paradoxical contraction of puborectalis. However, a positive EMG finding should trigger further definitive testing (e.g. defaecography), due to its low positive predictive value (31%) (Yeh et al. 2003).

It must be acknowledged that electromyographic testing has been nearly abandoned in contemporary practice, driven out by other (less invasive) diagnostic modalities.

1.4.4. Balloon expulsion test

If combined with manometry, the balloon expulsion test (BET) (Barnes and Lennard-Jones 1985) can assess rectoanal coordination during attempted defaecation. Intra-abdominal pressure raised above 80 mmHg in normal subjects allows successful expulsion of the balloon in a median of 50 seconds (Scott and Gladman 2008). According to the most frequently utilised technique, a deflated rubber balloon is placed in the rectum and inflated to 50 ml. The time taken to expulsion in the seated position is

recorded, with >1 minute considered as abnormal (Chiarioni et al. 2014), although different cut-offs have been proposed in previous studies. A recently published systematic review and metanalysis (Shah et al. 2018) did not show any significant difference in performance characteristics based upon expulsion time, therefore suggesting, for practical reasons, a normal cut-off of 1 min. However, other evidence has shown limitations of BET as a single test for diagnosis of dyssynergic defaecation or to rule out the necessity of biofeedback training (Lee et al. 2017). Indeed, it has become synonymous with dyssynergic defaecation, yet it can only show impaired evacuation.

1.4.5. Defaecography

Barium X-ray defaecography (BD) was originally described in the 1950s, where spots films were taken in patients with CC (Wallden 1952, Ekengren and Snellman 1953). Methodologic improvements refined the technique (Burhenne 1964, Wasserman 1964, Kerremans 1968, Robinson and Gibbons 1976, Ahlback and Broden 1978, Mellgren et al. 1994), allowing it to become popular in the 1980s (Mahieu et al. 1984) (Shorvon et al. 1989). BD has also been conducted using simultaneous administration of contrast agents into other organs (e.g. bladder, vagina, small intestine, or peritoneum) to overcome its inability to depict the perirectal soft tissues (Altringer et al. 1995, Bremmer et al. 1995). However, these steps inevitably increase the invasiveness of the examination, which also involves exposing the patient to ionizing radiation. Consequently, interest in utilising magnetic resonance imaging as an alternative modality by which to perform defaecography (MRID) has been increasing since its first report in 1991 (Kruyt et al. 1991, Yang et al. 1991).

Nevertheless, a consistent criticism of defaecography is the acknowledged overlap between health and disease (Palit et al. 2014), hampered by a paucity of normative data, which challenges our ability to define 'true' abnormalities. Even terminology is far from being universally accepted, given the numerous technical variations proposed and the plethora of synonyms of defaecography since its conception (Ekengren and Snellman 1953): 'cineradiographic defaecography' (Skomorowska et al. 1987), 'cinedefaecography' (Agachan et al. 1996), 'evacuating' (Poon et al. 1991) or 'evacuation' (Gladman et al. 2003) 'proctography', 'defaecation' (Hainsworth et al. 2017) or 'defaecating' (Thompson et al. 2002) 'proctography', 'videodefaecography' (Marti et al. 1999), and 'videoproctography' (Faucheron and Dubreuil 2000). The term 'defaecography' has been most commonly reported (~60% of all published articles), and was initially proposed by Mahieu to more clearly imply that the physiological act of 'defaecation' is examined in dynamic conditions analogous to the investigation of deglutition or micturition' (Bartolo et al. 1988). For the sake of simplicity, its use has been adopted in this thesis to designate both X-ray and magnetic resonance imaging techniques.

Defaecography is still considered as the reference standard for the assessment of pelvic floor disorders, given its capability to dynamically evaluate the rectum (and other pelvic organs) during attempted defaecation (Poncelet et al. 2017). Its advantage over BET and manometry is to enable characterisation of structural abnormalities (Palit et al. 2014, Palit et al. 2016). However, in the assessment of functional parameters (i.e. of recto-anal coordination during straining), there is still debate over which test should be considered the gold standard, especially in selecting patients who may be more likely

responsive to biofeedback therapy. Indeed, current evidence has showed considerable disagreement between the results of the 3 diagnostic modalities (Videlock et al. 2013, Palit et al. 2016). Despite a large body of data on the utility of barium X-ray defaecography (BD) in CC, standardized protocols and normative data are lacking. Questions thus remain over specific indications, which currently limits its role in guiding therapy for patients with CC.

1.4.6. Ultrasonography

Pelvic floor and anorectal ultrasonography is useful in the assessment of benign and malignant anorectal diseases. Over the last two decades, the use of pelvic floor ultrasound has been advocated as a cheaper, safer, and more tolerated radiologic technique compared to defaecography in the assessment of pelvic floor dysfunctions (Barthet et al. 2000). Two main methods have been described to dynamically assess the anorectum: 3-D echodefaecography and dynamic transperineal ultrasonography.

1.4.6.1. 3-D Echodefaecography (3DED)

3-D echodefaecography (3DED) was first described to assess anismus (Murad-Regadas et al. 2007). The automatic scan lasting 50 seconds captures axial sequential images (0.25 mm) resulting in a 3D volume displayed as a cubical image. This can be analysed in multiple planes, corresponding to real-time ultrasound imaging. A study comparing 3DED with BD showed similar diagnostic yield in detecting structural and functional abnormalities (Murad-Regadas et al. 2008).

1.4.6.2. Dynamic transperineal ultrasonography (DTPU)

Dynamic assessment of the pelvic floor by transperineal ultrasonography was first described by in 2001 (Piloni 2001). The procedure usually starts with the patient in the

left lateral position or in the dorsal lithotomy position. Bladder filling is useful for assessing the anterior compartment. The probe is positioned above the anus, in the midsagittal plane and the examination starts with the curved array probe for a gross evaluation.

DTPU is important in the anatomical, physiological and pathological evaluation of anorectal disorders, including obstructed defaecation, perianal inflammatory disease and faecal incontinence. Furthermore, it can well assess the anterior and mid compartments allowing a comprehensive evaluation of the pelvic floor (Hainsworth et al. 2015).

Two previous studies comparing DTPU with BD showed similar diagnostic yield in detecting structural abnormalities in males (Viscardi et al. 2012) and females (Martellucci and Naldini 2011) with ED.

1.5. Chronic constipation management overview

Management of CC is a major problem due to its high prevalence and lack of widespread specialist expertise. In general, a step-wise approach is undertaken, with lifestyle advices (optimising daily fluids/fibre intake and enhancing physical activities) and first-line conservative treatments (primary care) followed by nurse-led bowel re-training programmes, sometimes including focused biofeedback and psychosocial support (secondary/tertiary care) (Table 1.3).

TABLE 1.3 - BASIC TREATMENT OF CHRONIC CONSTIPATION.

MODIFIED FROM (KROGH ET AL. 2017)

Lifestyle modifications	Increased intake of fibre Sufficient intake of fluid Increased physical activity
First-line treatment	Oral laxatives:^ - Osmotic (e.g. lactulose, sorbitol, polyethylene-glycol) - Bulk-forming (e.g. psyllium, methylcellulose) - Lubricating (e.g. mineral oil) - Stimulant (e.g. bisacodyl, senna, sodium picosulfate) Rectal laxatives (suppositories or mini enema)*
Second-line treatment	Prokinetics (prucalopride) Secretory agents (linaclotide, lubiprostone) Biofeedback° Transanal irrigation§
^No data exist to recommend one oral laxative against others. **For patients with symptoms of evacuatory dysfunction.* *°For patients with dyssynergic defaecation* *§Mainly for patients with constipation secondary to neurological disorders.*	

Although biased by non-blinding, randomized controlled trials (RCT) published so far demonstrated major symptom improvement in 70%-80% of patients undergoing biofeedback for CC resistant to standard medical therapy and have determined it to be superior to polyethylene-glycol laxatives, diazepam or sham therapy; long-term studies have shown 55%-82% of patients maintain symptom improvement (Skardoon et al. 2017).

However, these treatments are very poorly standardised in the UK and are not universally successful. Patients with intractable symptoms and impaired QOL may subsequently be offered a range of costly, irreversible surgical interventions (e.g.

colectomy) with unpredictable results (Knowles et al. 1999, Knowles et al. 2009), sometimes resulting in major adverse events or a permanent stoma.

In some of these patients there is clinical and defaecographic evidence of a rectocoele and/or intussusception. These anatomical variants are considered to cause obstructed defaecation by a process of loss of force vector (ballooning of the rectum into a rectocoele or invagination of the rectum into an intussusception rather than evacuation of stool on straining) or mucosal obstruction (in the case of an intussusception) (D'Hoore and Penninckx 2003). It follows that clinical resolution of symptoms could be achieved by restoration of normal anatomy by surgery. Resuspension of the rectum aims to hitch the prolapsing or redundant rectal wall thus straightening the intussusception and/or effacing the rectocoele. This concept, while anatomically rational, remains clinically controversial for a number of reasons. First, such anatomical variants are common and are often found in healthy individuals with no symptoms of obstructed defaecation (Palit et al. 2014). Secondly, resuspension operations when employed to patients with full-thickness rectal prolapse (e.g. posterior rectopexy (Vantets and Kuijpers 1995)), may themselves cause increasing symptoms of obstructed defaecation (Tou et al. 2015). The potential for worsening constipation is thought to relate to fibrosis caused by insertion of foreign material, the creation of a fixed acute angulation at the rectosigmoid junction and mobilization of the lateral ligaments of the rectum. These ligaments contain nerves to the rectal wall and the resultant denervation may be the cause. In the process of developing alternative resuspending procedures, surgeons have attempted to limit the effect of the foreign material by using sutures only (Graf et al. 1996), added a resection of the sigmoid colon to the rectopexy (von Papen et al. 2007, Johnson et al. 2012) or

more recently, limiting the dissection of the rectum to the ventral surface by supporting the rectum with mesh (Faucheron et al. 2015). In addition, laparoscopy has become the favoured approach procedurally, not only allowing a more rapid recovery but also easing access to, and visibility in the pelvis.

As part of an NIHR-funded programme (PGfAR: RP-PG-0612-20001), Chronic Constipation Treatment PathwaY (CapaCiTY) aims to develop the evidence base for the management of chronic constipation in adults, which is currently lacking. This is in contrast to the management of CC in children, for which National Institute for Clinical Excellence (NICE) guidance has been already published (Bardisa-Ezcurra et al. 2010, Hooban 2010), and for adults with faecal incontinence (http://pathways.nice.org.uk/pathways/faecal-incontinence). Thus, there are considerable variations in practice, particularly in specialist services. With a number of new drugs gaining or seeking NHS approval (Camilleri et al. 2008, Lembo et al. 2010, Lembo et al. 2010, Lembo et al. 2011) and technologies at a horizon scanning stage (Knowles et al. 2009, Kamm et al. 2010, Maeda et al. 2010, Knowles et al. 2012), it is timely that the currently limited evidence base is developed for resource-constrained National Health System (NHS) providers to have confidence that new and sometimes expensive investigations and therapies are appropriate and cost-effective. A cost-conscious pathway of care may help reduce healthcare expenditures by appropriately sequencing the care provided, while targeting more expensive therapies at those most likely to benefit. Such data will inform the development and commissioning of integrated care pathways.

1.6. Gaps in current knowledge

Controversies exist in the diagnostic and therapeutic approach to CC patients. Significant disagreement has been shown between some of the current diagnostic modalities in the assessment of functional and structural abnormalities. Although traditionally considered a pathognomonic sign of anismus, the clinical significance of a negative RAPG on manometry has been questioned since the advent of high-resolution systems, which show a significant overlap between health and CC.

Although considered by many as first-line diagnostic tools (Carrington et al. 2018), the utility of the balloon expulsion test and anorectal manometry is very limited in the assessment of structural abnormalities as well as single tests in the assessment of functional abnormalities. Conversely, defaecography allows a thorough assessment of both features. However, its diagnostic yield in health and CC sufferers has not been investigated in detail.

Besides other available options in the surgical armamentarium, LVMR has been advocated for the treatment of external rectal prolapse in CC patients. Outcomes of LVMR in patients demonstrating obstructive intussusception are limited to observational studies, with no randomised controlled trials delivered so far.

1.7. Specific aims and hypotheses of the thesis

The aims and hypotheses of this thesis are to:

1. Explore the diagnostic accuracy of anorectal manometry for diagnosis of dyssynergic defaecation;

2. Examine the yield of defaecography in patients with CC and healthy volunteers through systematic review and meta-analysis;
3. Examine the prevalence of defaecographic structural and functional abnormalities in a single-centre series of consecutive constipation sufferers;
4. Explore outcomes of LVMR for symptomatic intussusception;
5. Contribute to protocol development for a stepped-wedge randomized controlled trial of LVMR for intussusception.

Chapter 2 - Diagnostic accuracy study of anorectal manometry for diagnosis of dyssynergic defaecation

2.1. Rationale

Functional constipation (FC) is a common disorder with a pooled prevalence in the community of 14% and significant cost and health care utilization (Suares and Ford 2011). Disordered defaecation, which is diagnosed by anorectal tests, is common in patients with medically-refractory chronic constipation (Cook et al. 2009, Ragg et al. 2011, Bharucha et al. 2013). The Rome III criteria for functional defaecation disorder (FDD) embrace the concept that impaired evacuation due to abnormal recto-anal coordination manifests as an abnormal recto-anal pressure gradient (RAPG, i.e. the difference between rectal and anal pressure), resulting from paradoxical contraction or inadequate relaxation of the pelvic floor muscles and/or to inadequate rectal propulsive forces during defaecation (Rao et al. 1999, Bharucha et al. 2006, Bharucha et al. 2006). To fulfil the Rome III diagnostic criteria for FDD, patients with FC must have evidence of two of the following criteria: (a) impaired evacuation; (b) inappropriate contraction of the pelvic floor muscles or <20% relaxation of basal resting pressure; (c) inadequate propulsive forces (Bharucha et al. 2006). While impaired evacuation is usually assessed by balloon expulsion (Chiarioni et al. 2014) or defaecographic imaging (Halligan et al. 2001, Palit et al. 2014), criteria (b) and (c) are assessed by measuring rectal and anal pressures during simulated evacuation (“push” manoeuvre) with anorectal manometry (AM) (Rao et al. 2002).

Several expert reviews provide guidance on technical performance and interpretation of AM (Rao et al. 2002, Scott and Gladman 2008). Based on limited data in asymptomatic participants in which rectal and anal pressures were simultaneously measured during the push manoeuvre (Rao et al. 1998, Rao et al. 1999), a negative RAPG (i.e. anal pressure exceeding rectal pressure) during simulated evacuation is used to help diagnose FDD. Four anal manometry (AM) patterns have been defined (Rao 2008), characterized by a paradoxical increase in anal pressure with (type I), or without (type II) adequate increase in rectal pressure, or failure of reduction in anal pressure with (type III), or without (type IV) adequate increase in rectal pressure.

With the advent of high-resolution manometry (Carrington et al. 2014), the ability of AM to distinguish healthy asymptomatic individuals from those with defaecatory symptoms has been questioned (Noelting et al. 2012), because contrary to conventional wisdom, the RAPG during simulated evacuation was negative) in a majority of asymptomatic women (Ratuapli et al. 2013). We therefore performed a prospective, blinded, assessment of anorectal pressure patterns in women with FC and asymptomatic women using high-resolution AM (HRAM). The conduct and reporting of this study applied STARD (standards for reporting diagnostic accuracy) criteria (Bossuyt et al. 2003). In the absence of a gold standard for diagnosis of dyssynergia (AM is the current standard), the specific aim was to evaluate the accuracy of AM (index test) in discriminating health from disease (this acting as a surrogate reference standard).

2.2. Methods

2.2.1 Study population

Consecutive female patients referred for investigation of CC over a 6-month period (June – December 2013) to the Royal London Hospital (Barts Health NHS Trust) GI Physiology Unit were considered for study enrolment. Healthy asymptomatic female volunteers (HV) were recruited by advertisement at Barts and the London School of Medicine and Dentistry during the same period. Prior to arriving for investigation, all participants (CC and HV) completed a comprehensive symptom questionnaire (Mohammed et al. 2010) incorporating the Cleveland Clinic Constipation score (CCCS) (Agachan et al. 1996). A structured history was also undertaken (medical/surgical and obstetric). Inclusion criteria for CC patients were a diagnosis of functional constipation based on Rome III symptom criteria (Longstreth et al. 2006), and scoring ≥12 on the CCCS as indication of severity. HV were selected on the basis of exclusion of any significant GI disease, self-reported functional symptoms, CCCS <9 and St Marks Incontinence Score <5 (Vaizey et al. 1999). Other exclusions included pregnancy or lactation, history of diabetes, cardiovascular, renal or hepatic disease. Ethical approval was granted by the Queen Mary University Research Ethics Committee (ref QMREC 2010/74 and QMREC 2013/12), and written informed consent obtained. No specific exclusions were applied for either group that might affect how the test itself performs (limited challenge bias) (Philbrick et al. 1980). The majority of CC patients also underwent further specialist evaluations including radio-opaque marker transit studies and barium defaecography (Palit et al. 2014).

2.2.2. Technical specifications (index test)

HRAM was performed in all participants using a solid-state catheter (UniTip: UniSensor AG, Switzerland), of external diameter 12 French, incorporating 12 microtransducers, each of which measured circumferential pressure by means of a unidirectional pressure sensor embedded within silicone gel. Ten of these sensors were spaced 0.8 cm apart, spanning 7.2 cm. The most proximal microtransducer was located within a non-latex balloon 3.3 cm proximal to these. The most distal sensor (located 2 cm below the most distal of the central 10 sensors) was used as an external reference. Before every study, the catheter was immersed in tepid water for at least 3 minutes to pre-wet the sensors. Sensors were then zeroed to atmospheric pressure. Data acquisition, online visualization and signal processing were performed using a commercially available manometric system (Solar GI HRM v9.1, Medical Measurement Systems (MMS), Enschede, Netherlands). Each participant was instructed to defaecate if required prior to investigation. No bowel preparation was given and all participants were studied in the left-lateral position with knees and hips flexed. Prior to catheter insertion, the ability of the participant to understand the commands “squeeze” and “push” were confirmed by digital rectal examination, the latter by asking the participant to “bear down as if to defaecate” (Carrington et al. 2014). All test manoeuvres were performed in accordance with published international minimum standards (Rao et al. 2002) using a previously published protocol (Carrington et al. 2014). The catheter was inserted into the anorectum with the distal 2 microtransducers visible (the second most distal being located immediately outside of the anal verge). Following a 3-minute run-in period for the purposes of stabilisation, manoeuvres were performed in a standard sequence with a 30 second recovery period between each. For examination of simulated defaecation

the participant was asked to “push” as practised for 5 seconds; this manoeuvre was performed twice (Rao et al. 2002). All tests were performed by one of three independent gastrointestinal physiology practitioners with experience of lower GI physiological testing.

Line-plot traces of rectal and anal pressure changes were extracted from individual HRAM pressure traces (approx. 3–6 sensors in the rectum, and approx. 4–7 spanning the anal canal depending on anal canal length) by an automated process, using the ‘e-sleeve’, or ‘area of interest’ function within the colour contour plot (HRM v9.1, Medical Measurement Systems). This is in accord with other recent HRAM methodological publications (Sauter et al. 2014). Rectal and anal line plots were automatically derived from the maximum pressure within each region at all recorded time points during the second push manoeuvre. This method was selected to avoid the implicit bias conferred by selecting what is often termed a ‘representative’ line plot (Rao et al. 2004). However, since such automated selection might confer a performance bias, original HRAM colour contour plots were also retained for analysis.

2.2.3. Definition, cut-offs and categories of the results of the index test

HRAM-derived line-plot images from both CC patients and HV were collated into a single database with all identifiers removed. Rectal and anal pressure changes (Rao 2008) during the second “push” manoeuvre from each individual were presented electronically in a computer generated random order. Images were circulated to three observers (writer included) who independently classified test results based on published criteria derived from standard manometry (Rao 2008) and expert international guidance (Rao et al. 2002) (Table 2.1).

TABLE 2.1 - DEFINITIONS OF MANOMETRIC PATTERNS DURING SIMULATED DEFAECATION.

Pattern	**Definition**
Normal	Adequate increase in rectal pressure (≥40mmHg) accompanied by simultaneous reduction in anal pressure
Type I dyssynergia	Adequate increase in rectal pressure (≥40mmHg) accompanied by paradoxical simultaneous increase in anal pressure
Type II dyssynergia	Inadequate increase in rectal pressure of (<40mmHg) (poor propulsive force) accompanied by paradoxical simultaneous increase in anal pressure
Type III dyssynergia	Adequate increase in rectal pressure (≥40mmHg) accompanied by failure of reduction in anal pressure (≤20% baseline pressure)
Type IV dyssynergia	Inadequate increase in rectal pressure of (<40mmHg) (poor propulsive force) accompanied by failure of reduction in anal pressure (≤20% baseline pressure)
Unclassified	Changes in rectal and anal pressure were not consistent with any of the above recognised patterns
Derived diagnoses	**Definition**
Failed anal relaxation	Any of 4 dyssynergia subtypes
FDD^	A combination of type II or type IV dyssynergia
^ *In patients with CC, both subtypes II and IV are independently sufficient to fulfil a diagnosis of functional defaecation disorder (FDD) without recourse to other tests (Bharucha et al. 2006).*	

To generate a final single result (for STARD analysis), disagreement between the 3 independent observers was resolved by consensus discussion mediated by the senior investigator.

The same methods were used to classify tracings according to recent criteria derived from HRAM (Ratuapli et al. 2013). In this classification, 2 phenotypes ("hybrid" and "low rectal") closely resemble types II and IV dyssynergia, respectively. A third novel ("high anal") pattern combined high anal pressures at rest and during evacuation (resembling the classical description of "anismus") (Preston and Lennard-Jones 1985). This phenotype was therefore also studied using the published cut-off of >92 mmHg to define high resting pressure (Ratuapli et al. 2013).

Finally, original HRAM colour contour plots were reviewed and classified by the same blinded multi-observer methodology.

2.2.4. Statistical analysis

All data were analysed in accord with STARD guidance (Bossuyt et al. 2003). Inter-observer agreement was determined using kappa statistics (Landis and Koch 1977). Proportions of CC and HV participants with each finding were compared using Chi-square test with Bonferroni correction for multiple comparisons. Standard diagnostic accuracy metrics were calculated and presented with confidence intervals (CI): test sensitivity and specificity; positive and negative predictive values (PPV and NPV) and likelihood ratios (LRs). LRs were interpreted according to standard definitions (McGee 2002). Post-hoc analysis was performed using software functions to generate mean values for raw pressure data. These were analysed between groups as continuous variables using student t-tests; receiver operating characteristic (ROC) curves were used

to explore diagnostic utility and optimal cut-offs. All data were analysed using Stata v10.0 (Stata Corporation, College Station, Texas, USA). Statistical significance was considered as $p < 0.05$ (excepting Bonferroni correction).

2.3. Results

2.3.1. Study population

A total 85 patients with chronic constipation (CC) and 85 healthy volunteers (HV) meeting selection criteria formed the study cohort. CC patients were slightly older than HV (mean age 46 vs. 42 years) and were more likely to be parous (82% vs. 59%). All FC patients had a CCCS ≥12 (median 17, interquartile range [IQR] 13-19) whereas no HV had a CCCS >5 (median 1, IQR 0-2). The findings for individual CCCS symptom domains and Rome III criteria for CC are shown in Table 2.2. All CC patients had symptomatic difficulty in evacuating stool from the rectum (Wald et al. 2014) and 21% had no relaxation or paradoxical contraction of puborectalis on digital rectal examination. Barium defaecography was performed in 81 CC patients (4 patients exceeded the equipment safety weight limit) of whom 59 (73%) had abnormal defaecatory function based on departmental control data (12 [15%] functional obstruction only, 33 [41%] dynamic structural obstruction only, 14 [17%] both) (Palit et al. 2014). Balloon expulsion testing was not performed reflecting local practice. Radio-opaque marker transit studies had been performed in 42/85 patients of whom 18 (43%) had delayed transit. Of these, 17 had concomitant defaecographic abnormalities (only one patient had generalised marker distribution and a normal defaecography).

TABLE 2.2 - CHARACTERISTICS OF THE STUDY POPULATION

Characteristics	HV N=85	CC N=85
Age (median, range)	41 (18-68)	46 (15-78)
Parity (number, %)	50 (58.8)	70 (82.4)
Self-reported constipation	0 (0)	85 (100)
CCCS (median, IQR)	1 (0-2)	17 (13-19)
Frequency of bowel movement	0 (0)	1 (0-2)
Painful evacuation effort	0 (0)	3 (2-4)
Feeling incomplete evacuation	0 (0-1)	4 (3-4)
Abdominal pain	0 (0-1)	3 (2-4)
Minutes in lavatory per attempt	0 (0)	2 (1-3)
Assistance for defaecation	0 (0)	1 (0-2)
Unsuccessful attempts per 24 hours	0 (0)	2 (2-3)
Duration of constipation in years	0 (0)	3 (1-4)
Rome III criteria for functional constipation (%)	0 (0)	85 (100)
Straining°	0 (0)	81 (95)
Lumpy or hard stool°	0 (0)	74 (87)
Feeling incomplete evacuation°	5 (5.9)	84 (99)
Feeling anorectal obstruction°	0 (0)	78 (92)
Manual manoeuvres°	0 (0)	42 (49)
<3 defaecations per week	0 (0)	62 (73)
Rare loose stool without laxatives	0 (0)	85 (100)
Insufficient criteria for IBS	85 (100)	85 (100)

HV: healthy volunteers; CC: patients with chronic constipation; IQR: interquartile range; CCCS: Cleveland Clinic constipation score. °Symptoms present in at least 25% of defaecations.

2.3.2. Performance of the index test: inter-observer agreement

Inter-observer agreement between the 3 primary investigators was substantial for diagnosis of FDD (k = 0.63; 144 / 170 [84.7%] traces had agreement of all 3 observers without need for consensus), types I (k=0.71) and IV dyssynergia (k=0.61); moderate for normal pattern (k=0.47) and dyssynergic patterns (failed anal relaxation [FAR]; k = 0.50); and fair for type II (k=0.40) and type III dyssynergia (k=0.35) (Table 2.3).

TABLE 2.3 - INTER-OBSERVER VARIABILITY IN THE DESCRIPTION OF LINE-PLOTS PATTERNS

Line-plots patterns	Observers	Kappa agreement	*p*
Normal	1 vs. 2	0.63	*
	1 vs. 3	0.46	*
	2 vs. 3	0.32	*
	Mean	0.47	
Type I dyssynergia	1 vs. 2	0.78	*
	1 vs. 3	0.64	*
	2 vs. 3	0.72	*
	Mean	0.71	
Type II dyssynergia	1 vs. 2	0.38	*
	1 vs. 3	0.48	*
	2 vs. 3	0.34	*
	Mean	0.40	
Type III dyssynergia	1 vs. 2	0.41	*
	1 vs. 3	0.38	*
	2 vs. 3	0.26	*
	Mean	0.35	
Type IV dyssynergia	1 vs. 2	0.63	*
	1 vs. 3	0.60	*
	2 vs. 3	0.58	*
	Mean	0.61	
Types I-IV (FAR)	1 vs. 2	0.69	*
	1 vs. 3	0.46	*
	2 vs. 3	0.36	*
	Mean	0.50	
Types II + IV (FDD)	1 vs. 2	0.75	*
	1 vs. 3	0.60	*
	2 vs. 3	0.54	*
	Mean	0.63	

FAR: failed anal relaxation; FDD: functional defaecation disorder.
**p* <.001.

2.3.3. Performance of the index test against the reference standard: diagnostic accuracy (Figure 2.1)

Based on results of consensus, more than 90% of all participants showed an abnormal pattern of rectoanal coordination during attempted defaecation (Table 2.4; Figure 2.2A).

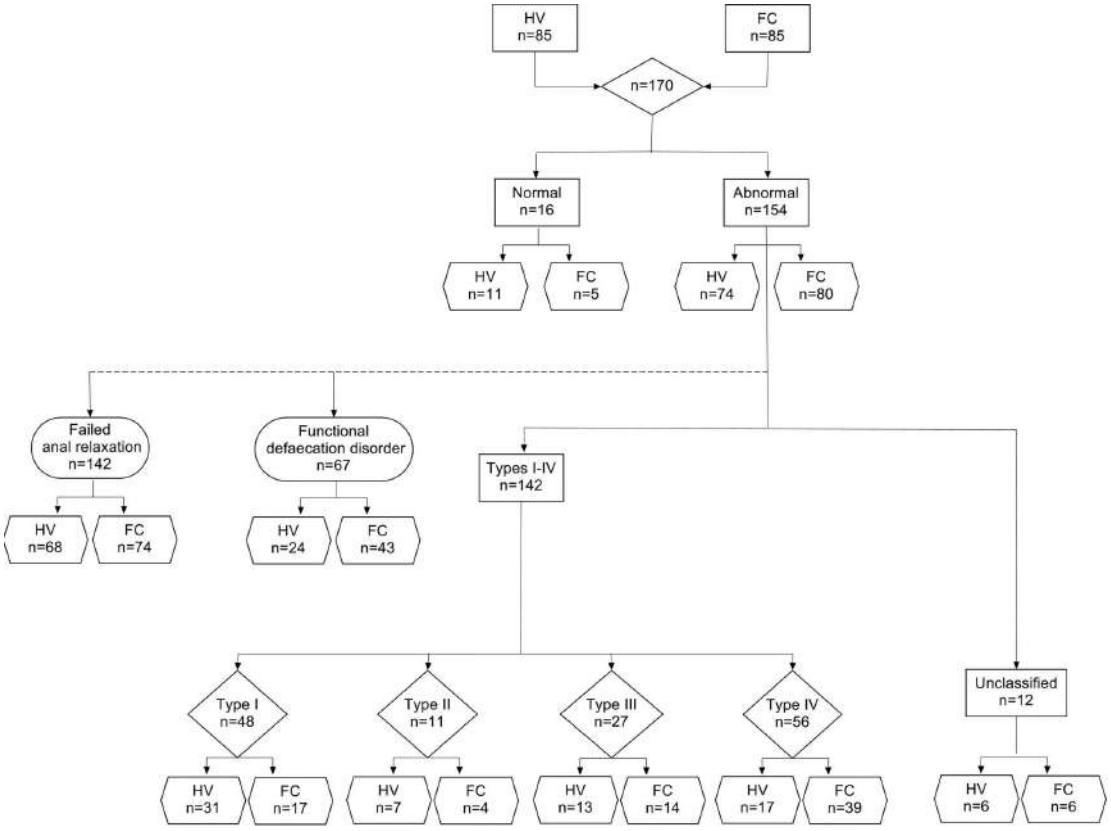


FIGURE 2.1 - STANDARDS FOR REPORTING OF DIAGNOSTIC ACCURACY (STARD) FLOWCHART DETAILING THE STUDY PROFILE. HV: HEALTHY VOLUNTEERS; FC: PATIENTS WITH FUNCTIONAL CONSTIPATION.

TABLE 2.4 - DISTRIBUTION OF DYSSYNERGIC PATTERNS IN THE STUDY POPULATION AFTER CONSENSUS

Line-plot patterns	**All N=170**	**HV N=85**	**CC N=85**	***p***
Abnormal	154 (91)	74 (87)	80 (94)	.19
Type I dyssynergia	48 (28)	31 (37)	17 (20)	.03
Type II dyssynergia	11 (6)	7 (8)	4 (5)	.53
Type III dyssynergia	27 (16)	13 (15)	14 (17)	1
Type IV dyssynergia	56 (33)	17 (20)	39 (46)	.001*
Unclassified	12 (7)	6 (7)	6 (7)	1
Types I-IV (FAR)	142 (84)	68 (80)	74 (87)	.30
Types II + IV (FDD)	67 (39)	24 (28)	43 (51)	.005**

HV: healthy volunteers; CC: patients with chronic constipation; FAR: failed anal relaxation; FDD: functional defaecation disorder. Values in parenthesis are percentages.
** Bonferroni correction requires p≤0.008; ** Bonferroni correction requires p≤0.003*

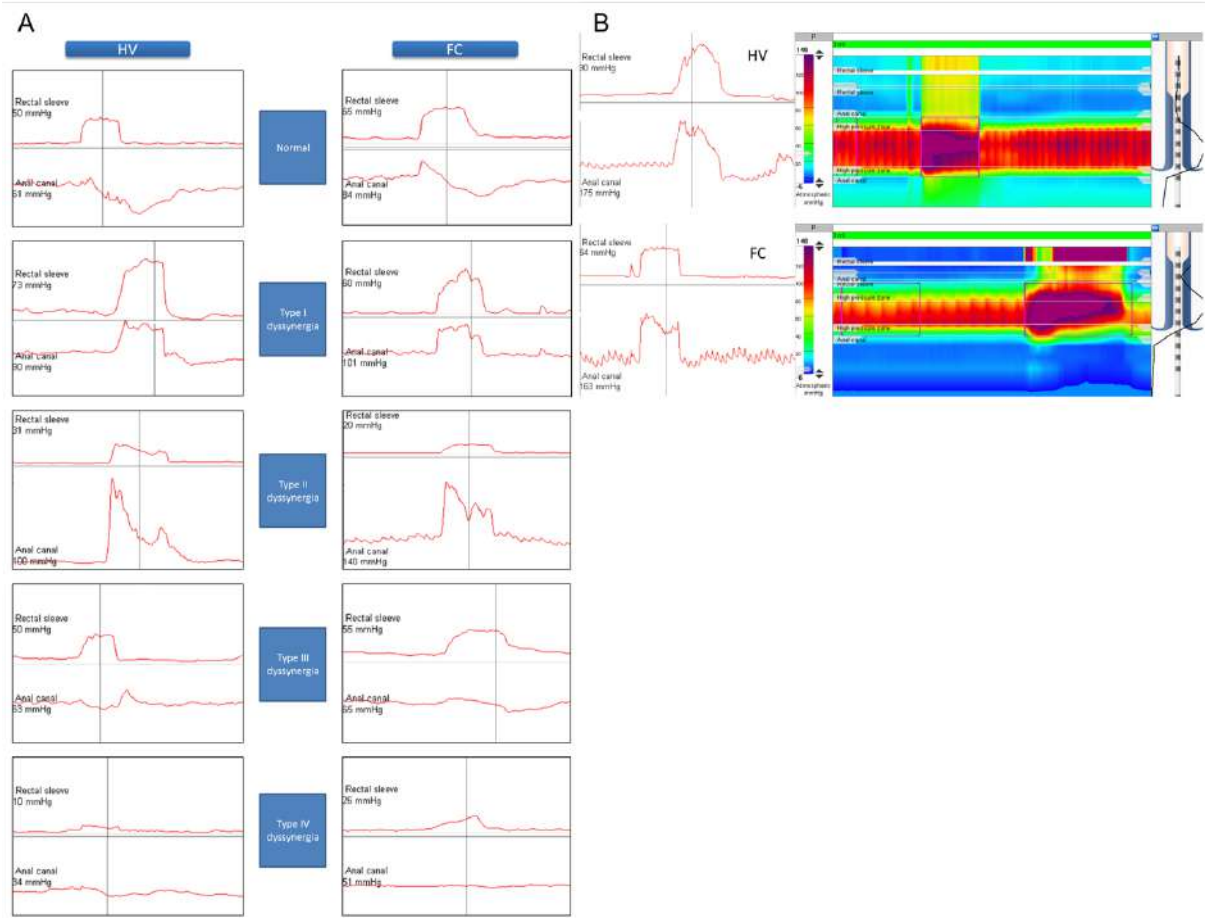


FIGURE 2.2 - (A) EXAMPLES OF LINE-PLOT PATTERNS IN THE STUDY POPULATION AFTER CONSENSUS. (B) HIGH ANAL PHENOTYPE IN A PATIENT WITH CHRONIC CONSTIPATION (CC) AND HEALTHY VOLUNTEERS (HV) AS LINE PLOTS AND RAW COLOUR CONTOUR TRACE.

A slightly higher proportion of patients with CC compared to HV (94 vs. 87%) had abnormal findings. The prevalence of type I dyssynergia was more than 80% greater in HV than CC. The prevalence of types II and III dyssynergia was comparable in HV and FC. Only type IV dyssynergia was found significantly more frequently in CC patients (46% CC patients vs. 20% HV, p=0.001). Based on synthesis of subtypes II and IV, 51% CC patients fulfilled AM criteria for FDD vs. 28% of HV (p=0.005). Seven percent of participants showed an inadequate increase in rectal pressure of <40mmHg (poor propulsive force), accompanied by a simultaneous reduction in anal pressure. Such changes are not

consistent with any recognised patterns (Rao 2008) deriving a fifth category (Bertiaux-Vandaele et al. 2011). This 'unclassified' pattern was equally encountered in CC patients and HV. These results were consistent regardless of individual observer.

The diagnostic accuracy for discriminating between FC and HV was poor (Table 2.5). Only type IV dyssynergia had a positive likelihood ratio of 2.3 indicative of a 'small' increase in the likelihood of disease (McGee 2002). Others suggested no (LR: 0.5-1.0) or minimal increase (LR: 1.0-2.0) in disease likelihood. These measures of diagnostic accuracy were comparable across observers.

TABLE 2.5 - SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE VALUE (PPV), NEGATIVE PREDICTIVE VALUE (NPV) AND POSITIVE LIKELIHOOD RATIO (LR+) OF HRAM FOR DIAGNOSIS DYSSYNERGIC SUBTYPES AND FDD.

Line-plot patterns	Sensitivity	Specificity	PPV	NPV	LR+
Abnormal	94.1	12.9	51.9	68.8	1.1
Type I dyssynergia	20.0	63.5	35.4	44.3	0.6
Type II dyssynergia	4.7	91.8	36.4	49.1	0.6
Type III dyssynergia	16.5	84.7	51.9	50.3	1.1
Type IV dyssynergia	45.9	80.0	69.6	59.6	2.3
Types I-IV (FAR)	87.1	20.0	52.1	60.1	1.1
Types II + IV (FDD)	50.6	71.8	64.2	59.2	1.8

FAR: failed anal relaxation; FDD: functional defaecation disorder.
All values, except LR+, expressed as percentages.

2.3.4. Performance of the index test using new HRAM criteria (Ratuapli et al. 2013) and post-hoc data analysis

Overall, 13% of participants had the "high anal" phenotype (Ratuapli et al. 2013) (Figure 2.2C), which was more frequent in CC patients (14/85 [17%]) than in HV (8/85 [9%]). However, differences were not significant (p=0.25). Considering the poor diagnostic

accuracy of HRAM using published pattern-based criteria, software functions were used to generate mean values for relevant variables: resting anal pressure; push rectal pressure, anal pressure change and RAPG during push manoeuvres (Table 2.6).

TABLE 2.6 - POST-HOC ANALYSIS OF RAW SOFTWARE-DERIVED DATA FOR DEFAECATORY PRESSURE VARIABLES

Variable	**HV** Mean (SD)	**CC** Mean (SD)	**p-value** (t-test)	**ROC curves** AUC (CI)
Mean resting pressure	64.5 (21.1)	62.7 (25.8)	0.31	0.519 (0.43-0.61)
Push rectal pressure	42.3 (19.0)	30.3 (17.2)	0.0001	0.675 (0.59-0.76)
Push anal pressure change	-9.2 (18.9)	-6.1 (15.5)	0.88	0.425 (0.34-0.51)
Rectoanal pressure gradient	-13.4 (26.9)	-26.3 (24.3)	0.0007	0.639 (0.56-0.72)

HV: healthy volunteers; CC: patients with chronic constipation; SD: standard deviation; ROC receiver operating characteristic; AUC: area under the curve; CI: confidence interval.

In keeping with earlier analyses, differences in anal sphincter relaxation during the push manoeuvre between healthy volunteers and patients were not significant (p=0.88). The RAPG was found to be negative (i.e. <0 mmHg) for most (84%) participants regardless of health status (median, -18 mmHg; IQR, -38 to +1). However, a greater proportion of HV than CC patients (32/85 [38%] vs. 13/85 [15%]: OR 0.31 [CI 0.15-0.65]; p=0.002) had a positive RAPG (i.e. ≥0 mmHg). ROC curves of RAPG and push rectal pressure had an area of 0.639 and 0.675 respectively for discriminating between CC and HV (Figure 2.3). Furthermore, CC patients quantitatively had a significant poorer rectal 'push' pressure (i.e. propulsive force, p=0.0001).

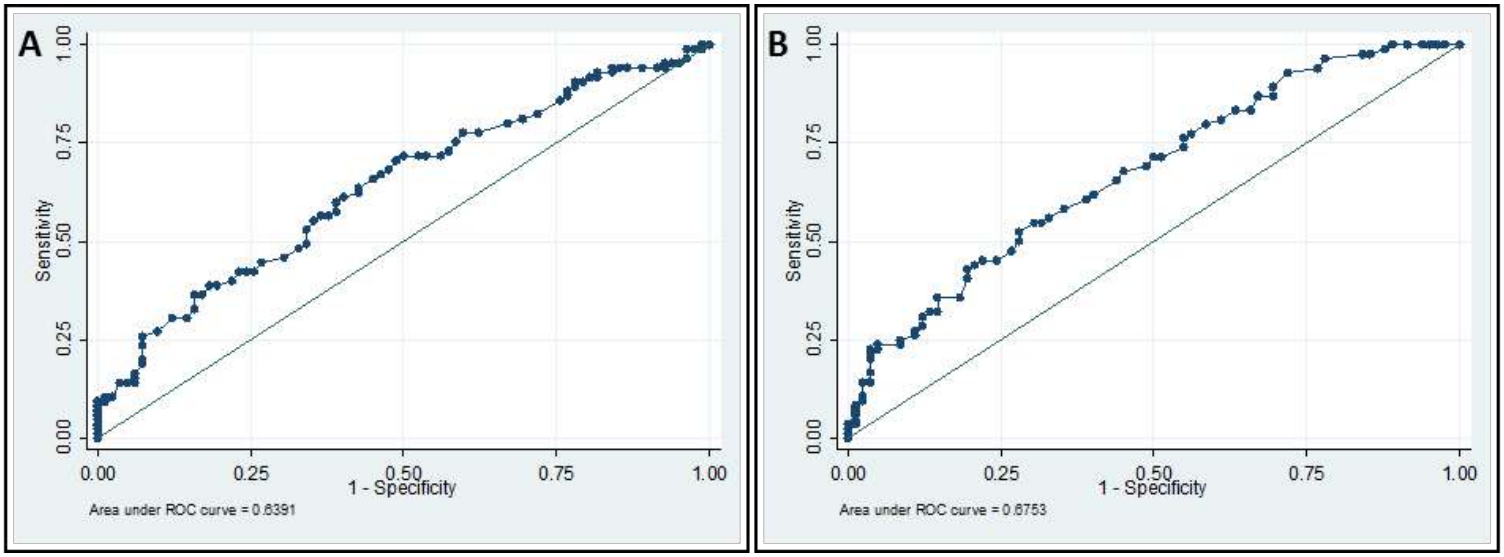


FIGURE 2.3 - RECEIVER OPERATING CHARACTERISTIC (ROC) CURVES FOR RECTOANAL PRESSURE GRADIENT (A) AND MEAN RECTAL PRESSURE (B) IN HV AND CC PATIENTS DURING SIMULATED DEFAECATION (AREA UNDER THE CURVE [AUC]: 0.639 AND 0.675, RESPECTIVELY).

For the push rectal pressure, cut-offs of less than 40mmHg (Rao 2008) and ≤45mmHg (Rao et al. 2004) were most useful (i.e., sensitivity 53% and 43%; specificity 72% and 81%, respectively) for discriminating between CC and HV. Both parameters correctly identified 62% of patient's health status.

Using identical analytical methodology for HRAM colour contour plots yielded almost identical results.

2.4. Discussion

There are four main observations in this study. First, among experienced practitioners, inter-observer reproducibility for interpreting anorectal pressure patterns during simulated evacuation was acceptable. Second, only 9% of all participants exhibited the accepted (Rao et al. 1998) 'normal' pattern of rectoanal coordination (i.e. an 'adequate' increase in rectal pressure, accompanied by a simultaneous reduction in anal pressure). Third, 94% of CC patients and 87% of HV had abnormal manometric patterns during simulated defaecation; this difference was not statistically significant. Four, some individual patterns discriminated CC from HV, e.g. the type IV pattern was modestly useful (i.e., PPV 70%, LR+ 2.3). Also, subtypes II and IV, which are both characterised by inadequate sphincter relaxation and poor propulsion, were observed in 51% CC patients vs. 28% of HV with a LR+ of 1.8. The 'high anal' phenotype, which is only based on anal pressure, was also found more commonly in CC patients (17%) than HV (9%). Hence, measures that rely on the rectal pressure generated during the push manoeuvre were more useful than those that rely on anal pressure alone for discriminating between CC and HV. These findings have implications on the diagnosis and understanding of the pathogenesis of FDD.

2.4.1. Anal sphincter dyssynergia

The term dyssynergia originated in urology in the mid-1970s (Andersen and Bradley 1976) and was first used in the context of defaecation in 1992 (Merkel and Wald 1992). Implicit in the term is the failure of coordinated changes in anal sphincter activity. The current study refutes the concept that either a failure of anal relaxation or paradoxical anal contraction, as measured by high resolution AM, are of pathophysiological significance: these findings were present in 87% of CC patients and 80% of HV and there was no difference in absolute pressure data between groups (p=0.88). This finding is not novel. Indeed, the specificity of 'anismus' (Preston and Lennard-Jones 1985), defined solely by recruitment of EMG activity, has been questioned by more recent studies (Roberts et al. 1992, Schouten et al. 1997). Nevertheless, accepting significant historical differences in methodology, dyssynergia identified by manometry is widely used to diagnose FDD (Kerrigan et al. 1989, Wald et al. 1990, Roberts et al. 1992, Merkel et al. 1993) (Table 2.7). However, it is generally recognized that these studies included relatively small numbers of participants (particularly healthy) while others were uncontrolled (Rao et al. 2004). Moreover, no previous study has performed blinded assessment of AM tracings or evaluated inter-observer reproducibility. Despite these limitations, rectoanal pressure patterns during evacuation are recommended to diagnose and classify FDD (Bharucha et al. 2006, Rao 2008).

The recently described 'high anal' phenotype (Ratuapli et al. 2013), characterized by high anal pressures at rest and during evacuation, closely resembles classical 'anismus' (Preston and Lennard-Jones 1985), and might be useful for discriminating between HV and CC. The current study, which evaluated these parameters on an independent sample, showed that while the pattern was not common (13%), it was approximately

twice as frequent in CC patients compared to HV. Interestingly, the upper 90% percentile of the current HV dataset was 91 mmHg and therefore almost identical to the published anismus literature (92mmHg) (Ratuapli et al. 2013). Comparison of these data with those obtained by modern techniques has obvious limitations, however this finding still lends support to the use of the 90th percentile cut-off which was used to define the 'high anal' phenotype in the Ratuapli study (Ratuapli et al. 2013) and suggests that anal dyssynergia in the context of very high resting pressures may have some diagnostic utility.

TABLE 2.7 - PREVALENCE OF DYSSYNERGIC DEFAECATION IN HEALTHY VOLUNTEERS (HV) AND PATIENTS WITH CONSTIPATION (CC) BASED ON MANOMETRIC CRITERIA

Authors, Year	HV/CC	Prevalence of dyssynergic defaecation (%) *		Blinding	Age/Sex matching
		HV	CC		
Barnes, 1988	15/31	20	97	No	No
Kerrigan, 1989	29/16	12	73	No	Yes
Wald, 1990	12/36	8	31	No	Yes
Roberts, 1992	20/71	5	24	No	No
Merkel, 1993	17/18	12	50	No	No
Voderholzer, 1997	18/102	22	41	No	No
Rao, 1998	25/35	20	51	No	No
Ratuapli, 2013	62/295	82	92	No	Yes
Present study	85/85	80	87	Yes	Yes

** Different criteria were used for diagnosis: paradoxical sphincter contraction or failed anal relaxation (Barnes and Lennard-Jones 1988, Kerrigan et al. 1989, Wald et al. 1990, Merkel et al. 1993, Voderholzer et al. 1997), inability to raise intra-rectal pressure (Roberts et al. 1992), negative RAPG (Rao et al. 1998, Ratuapli et al. 2013) during simulated evacuation. In one study (Roberts et al. 1992), the diagnosis was based on the combination of electromyographic recruitment >50%, evidence of an adequate intra-rectal pressure on straining (>50 cmH_2O) and defective evacuation (either quantitatively or in terms of prolonged straining).*

2.4.2. Rectoanal pressure gradient (RAPG)

The RAPG is a function of both rectal propulsive effort and anal relaxation. Half a century ago, Harris *et al* (Harris and Pope 1964), observed that the RAPG during Valsalva manoeuvre was negative (i.e. sphincter pressures exceeded rectal pressures) in each of 41 times this manoeuvre was performed in 15 healthy males. This finding was confirmed by Phillips *et al* (Phillips and Edwards 1965), who showed that sphincter-ampulla pressure gradient was sustained despite rising intra-abdominal pressure by bearing down in 39 healthy volunteers. More recently, studies using high-resolution methods (Noelting et al. 2012, Ratuapli et al. 2013) have also demonstrated that the RAPG was negative in 51/62 (82%) asymptomatic women regardless of age (≥ or <50 years) and that there was considerable overlap in gradient between asymptomatic participants and constipated patients with abnormal balloon expulsion times. The current study is in keeping with the latter findings with 79% of all participants showing a negative RAPG. Although this variable did significantly differ between CC and HV ($p=0.0007$), the relatively similar proportions of participants with a negative RAPG (CC patients: 85% vs. HV: 62%) would confer limited utility of this variable to distinguish health from disease in practice. This presents an obvious conundrum for the current understanding of defaecation. One explanation for this observation was recently provided by Sauter et al. (2014), who hypothesise that simulated defaecation may drive the recording catheter against the wall of the anal canal producing a 'contact pressure', increase that may result in a negative RAPG.

2.4.3. Rectal propulsive force

The current study showed no differences in anal pressure changes between CC patients and HV but some differences in RAPG. This can only be explained by differences in rectal pressure during simulated defaecation (the term 'rectal propulsive force' is generally applied to this phenomenon although force and acceleration are not actually measured) and was confirmed by results (positive likelihood ratio for type IV dyssynergia) and post-hoc analysis of raw data ($p=0.0001$; AUC 0.673). This finding also agrees with the principal components analysis performed by Ratuapli *et al* (Ratuapli et al. 2013), in which a 'low rectal' phenotype was identified with close resemblance to type IV dyssynergia. Interestingly, ROC analysis of data from the current study also showed that the two cited cut-offs for type IV dyssynergia (40mmHg and 45mmHg) match exactly those from published diagnostic criteria for low rectal pressure (Rao et al. 2004, Rao 2008).

The discrepancy between the current results and some previous studies (especially for sphincter dyssynergia) is hard to explain but could reflect anxiety in the laboratory setting (Duthie and Bartolo 1992, Rao et al. 2006), the challenge of replicating the process of defaecation in the left lateral position with an empty rectum (Rao et al. 1998, Rao et al. 1999), or variable equipment and protocols (Carrington et al. 2014). Rao *et al* (Rao et al. 2006) evaluated rectal expulsion of balloon and a stool substitute with synchronous rectoanal pressures during evacuation in the left lateral and seated positions in 25 healthy participants. They showed that the RAPG during simulated defaecation and rectal pressures were higher in the seated than the left lateral position: 36% of asymptomatic participants had dyssynergia during traditional manometry in the recumbent position compared to 20% in the seated position ($p<0.05$). HRAM pressures

during balloon expulsion performed in the seated and left lateral positions have also been compared in 220 women (Ratuapli et al. 2013) Although rectoanal pressures were not evaluated in the seated position, the RAPG in participants with normal balloon expulsion in both positions was progressively more negative in those with abnormal balloon expulsion in recumbent only, seated only, and both positions. The current study only evaluated participants in the left lateral position and using the recommended minimum standard of 2 attempts at 5 second 'push'. Although this is common current practice (Rao et al. 2002, Carrington et al. 2014), the results emphasize that important test variables such as subject position and protocol (e.g. number and duration of push attempts) would benefit from international standardisation. The use of an automated 'area of interest' function was in accord with a recent HRAM methodological publication (Sauter et al. 2014) but is also a potential source of variation from user-selected 'representative' line plots (Rao et al. 1998). To counter this potential criticism, we repeated all analyses using complete HRAM colour contour plots i.e. without restricting analysis to a single sensor-derived line trace. These results, based on a summative global impression of anal and rectal pressure profiles, however yielded identical conclusions (Table 2.8).

TABLE 2.8 - DISTRIBUTION OF DYSSYNERGIC PATTERNS IN THE STUDY POPULATION AFTER CONSENSUS (HIGH-RESOLUTION ANORECTAL MANOMETRY [HRAM] COLOUR CONTOUR PLOTS).

HRAM patterns	All N=170	HV N=85	FC N=85	*P*
Abnormal	158 (93)	77 (91)	81 (95)	.37
Type I dyssynergia	78 (46)	45 (53)	33 (39)	.09
Type II dyssynergia	9 (5)	5 (6)	4 (5)	1
Type III dyssynergia	36 (21)	19 (22)	17 (20)	.85
Type IV dyssynergia	31 (18)	7 (8)	24 (28)	.001*
Unclassified	4 (2)	1 (1)	3 (4)	.62
Types I-IV (FAR)	154 (91)	76 (89)	78 (92)	.79
Types II + IV (FDD)	40 (24)	12 (14)	28 (33)	.007**

HV: healthy volunteers; FC: patients with functional constipation; FAR: failed anal relaxation; FDD: functional defaecation disorder. Values in parenthesis are percentages.
** Bonferroni correction requires p≤0.008; ** Bonferroni correction requires p≤0.003.*

2.4.4. Limitations

Despite attempts to reduce performance bias by study design and adherence to STARD guidance, there were still some weaknesses in the current study. First, it must be acknowledged that health status as a reference standard can only be considered a surrogate of the notional concept of a positive RAPG. This approach had to be taken, since anal manometry is (in current practice) the most used tool to measure sphincter pressures without inclusion of more invasive (and themselves questionable) methods, e.g. needle EMG (Bharucha and Rao 2014). The FC patients studied all met symptomatic criteria for a defaecation disorder as defined by recent ACG guidance (Wald et al. 2014)

and severity criteria based on Cleveland clinic score cut-off of 12 points (Agachan et al. 1996). The majority of those tested (73%) also had evidence of impaired evacuation on barium defaecography. Further, only one patient had a generalised disturbance of colonic transit in the absence of abnormal defaecography, i.e. a probable primary disturbance of colonic motility. While the use of the balloon expulsion test may have provided further phenotypic information in the patient cohort as in other recent studies that show concordance between balloon expulsion time and dyssynergia (Minguez et al. 2004, Chiarioni et al. 2014), it must be recognised that the main driver of poor manometric discriminant ability was not the failure to 'enrich' or limit the CC population to those with perfectly-defined defaecatory dysfunction, but rather the observation that a similar majority of HVs also had evidence of dyssynergic defaecation.

Secondly, the definition of reference standard was made before the index test; this is a weakness which makes the index test in effect retrospective but a necessary feature of design. It would be impractical to recruit participants of unknown health status for HRAM testing and use the test result to predict symptom status because only a minority would have constipation due to defaecatory dysfunction. Nevertheless, investigations and their interpretation were performed completely blind to health status by multiple observers who reached almost identical conclusions. Finally, while HRAM trace interpretation was completely blind to health status, all 3 observers were aware that the overall data set contained an equal mix of 85 CC patients and 85 HV participants. However, this equal split did not appear to influence the observers, one of whom defined nearly all presented traces (95%) as abnormal. It seems unlikely that the current study results are not purely a function of the new technology given the success of HRAM

methods and their almost universal adoption in the study of oesophageal function (Bredenoord et al. 2012) (an organ with much functional homology to the anorectum).

2.4.5. Clinical significance

The results of this study do not completely negate the value of AM in the diagnosis of FDD and subtypes. Rather, integration of the pattern classification systems proposed by Rao *et al* (Rao 2008), the new physiological phenotypes proposed by Ratuapli *et al* (Ratuapli et al. 2013) and the current data provides for potential modification of existing disease classification and guidance. In summary:

1. Anal sphincter dyssynergia is not a pathophysiological finding except in the relatively small proportion of patients in which this is accompanied by high resting tone. With some systems, the cut-off of 92 mmHg (Ratuapli et al. 2013) to define high resting pressure appears valid.

2. Type IV dyssynergia (Rao 2008) is useful for distinguishing disease from health. Either of the published cut-offs (<40 (Rao 2008) or ≤45mmHg (Rao et al. 2004)) are valid for defining low rectal propulsive pressure. The dominant effect of poor rectal propulsive pressure in the current study suggests that the previously proposed 'low rectal' phenotype (Ratuapli et al. 2013) may be a more appropriate diagnostic term.

Further, the results do not negate the value of AM in the management of CC. AM is used with integrated balloon catheters to guide behavioural therapy using direct visual biofeedback with numerous trials attesting to the general success of this therapeutic approach (Heymen et al. 2007, Rao et al. 2007, Rao et al. 2010) with associated increases in RAPG, reflecting improved rectoanal coordination (Rao et al. 1998). The current study did not evaluate this role for AM.

In conclusion, the present data obtained by blinded multi-observer assessment, and in a relatively large sample size, suggest that the interpretation of AM patterns is reproducible. However, nearly 90% of HV have a pattern that is currently regarded as 'abnormal' by AM. Hence, AM is of limited utility for distinguishing between CC and HV. Taken together with other recent studies (Noelting et al. 2012, Ratuapli et al. 2013), these findings reinforce the need to re-evaluate the role of AM with high resolution or high definition catheter systems (Lee et al. 2013) for diagnosing dyssynergic defaecation.

Chapter 3 - Defaecography should be the first-line diagnostic modality in patients with refractory constipation: implications from a systematic review and meta-analysis.

4.1. Background

Chronic constipation (CC) affects up to 14% of the general population in Western countries (Suares and Ford 2011), with pathophysiology commonly accepted as an overlap between slow colonic transit and/or an evacuation disorder (ED) (Rao et al. 2016). ED may result from 'structural' causes (e.g. intussusception, rectocoele, enterocoele) and/or 'functional' disorders (e.g. impaired recto-anal coordination) of the anorectal region (Bharucha and Rao 2014). As symptoms alone do not reliably discriminate between CC subtypes, anorectal radiophysiological testing are usually warranted in those patients with refractory symptoms (Lembo and Camilleri 2003). The balloon expulsion test (BET), anorectal manometry, and defaecography represent the 3 main diagnostic modalities (Bharucha and Rao 2014). BET and manometry are currently considered the first-line tests (Wald et al. 2014), but *de facto* these do not provide any information on structural abnormalities that may impede evacuation.

Defaecography is a radiologic technique still considered as the reference standard for the assessment of pelvic floor disorders, given its capability to dynamically evaluate the rectum (and other pelvic organs) during simulated defaecation (Poncelet et al. 2017). Its particular advantage over BET and manometry is that it enables characterisation of

structural abnormalities (Palit et al. 2014, Palit et al. 2016). However, in the assessment of functional parameters (i.e. of recto-anal coordination during straining), there is still debate over which test should be considered the gold standard, especially in selecting patients who may be more likely responsive to biofeedback therapy. Indeed, current evidence has shown considerable disagreement between the results of the three diagnostic modalities (Videlock et al. 2013, Palit et al. 2016).

3.2. Historical perspective and terminology

X-ray barium defaecography (BD) was originally described in the 1950s, where spot films were taken in patients with CC (Wallden 1952, Ekengren and Snellman 1953). Methodologic improvements refined the technique (Burhenne 1964, Wasserman 1964, Kerremans 1968, Robinson and Gibbons 1976, Ahlback and Broden 1978, Mellgren et al. 1994), whereby it has become more routinely available since the 1980s (Mahieu et al. 1984) (Shorvon et al. 1989). BD has also been conducted using simultaneous administration of contrast agents into other organs (e.g. bladder, vagina, small intestine, or peritoneum) to overcome its inability to depict the perirectal soft tissues (Altringer et al. 1995, Bremmer et al. 1995). However, these steps inevitably increase the invasiveness of the examination, which also involves exposing the patient to ionizing radiation. Consequently, interest in utilising magnetic resonance imaging as an alternative modality by which to perform defaecography (MRID) has been increasing since its first report in 1991 (Kruyt et al. 1991, Yang et al. 1991).

Regardless of technique, a consistent criticism of defaecography is the acknowledged overlap between health and disease (Palit et al. 2014), hampered by a paucity of normative data, which challenges our ability to define ‘true’ abnormalities. Even

terminology is far from being universally accepted, given the numerous technical variations proposed and the plethora of synonyms of defaecography since its conception (Ekengren and Snellman 1953): 'cineradiographic defaecography' (Skomorowska et al. 1987), 'cinedefaecography' (Agachan et al. 1996), 'evacuating' (Poon et al. 1991) or 'evacuation' (Gladman et al. 2003) 'proctography', 'defaecation' (Hainsworth et al. 2017) or 'defaecating' (Thompson et al. 2002) 'proctography', 'videodefaaecography' (Marti et al. 1999), and 'videoproctography' (Faucheron and Dubreuil 2000). The term 'defaecography' has been most commonly reported (~60% of all published articles), and was initially proposed by Mahieu to more clearly imply that the physiological act of 'defaecation' is examined in dynamic conditions analogous to the investigation of deglutition or micturition' (Bartolo et al. 1988). For the sake of simplicity, we have adopted its use in the manuscript to designate both X-ray and magnetic resonance imaging techniques.

3.3. Technique

3.3.1. X-ray barium defaecography (BD)

The first symposium on BD, in 1988, brought together the knowledge of 10 experts from 6 tertiary centres across the world (United Kingdom, Sweden, The Netherlands, Belgium, United States, and Canada) (Bartolo et al. 1988). Considerable variation in technique was immediately apparent, in terms of patient position, bowel preparation, consistency of contrast materials, types of radiolucent commode, definitions of normality and abnormality and their clinical implications. Surprisingly, most of these variations have continued to the present, as discussed below.

Beside the rectum, opacification can be extended to vagina, bladder and/or small bowel. A viscous contrast material is routinely used to achieve a consistency similar to stool. Proprietary commercial formulations are available (e.g. 100% weight for volume barium sulphate agent Anatrast® [E-Z-EM, Westbury, NY]) to be administered via a caulking gun. Alternatively, homemade physiological pastes are preferred by some institutions using organic ingredients (e.g. potato and oatmeal mixes), which then have barium added. Thick barium (10 ml to 30 ml) or soaked tampons have been utilized for vaginal opacification. Barium suspension (100 ml to 500 ml) has also been administered orally for small bowel opacification. In 4 studies, bladder opacification was achieved using 50-250 ml of iodinated, radiopaque contrast medium (Mellgren et al. 1998, Boccasanta et al. 2010, Boenicke et al. 2011, Kassis et al. 2015). Conventional BD exposes patients to a mean radiation equivalent dose of 0.5-5.0 millisieverts and a gonadal (equivalent) radiation dose of approximately 20-25 millisieverts in female patients (Goei and Kemerink 1990, Zonca et al. 1997, Palit et al. 2014).

3.3.2. Magnetic resonance imaging defaecography (MRID)

The role of MRID in the evaluation of pelvic floor disorders has been less extensively investigated. The obvious advantage over BD is the ability of MRID to simultaneously assess the three pelvic compartments with good accuracy, without ionising radiation, and with limited invasiveness or discomfort (Maccioni 2013). However, MRID is usually performed using closed 1.5 Tesla magnets with the patient supine, which is often criticised as non-physiological (Maglinte and Bartram 2007, Maglinte et al. 2011). Although MRID can also be performed with an open magnet (thus allowing a physiological sitting position), initial comparative studies between open and closed

systems showed reasonable concordance of findings, hence validating the widespread use of the latter (Bertschinger et al. 2002). Nevertheless, more recent evidence suggests that MRID using closed-magnet systems, with the patient in a supine position, overestimates the grade of the dynamic descent of the pelvic floor (Iacobellis et al. 2016) and, at the same time, may result in underestimation of the severity of all disorders compared to open-magnet with the patient in a sitting position (Gatta et al. 2013).

As with BD, MRID lacks technical standardization of equipment, available sequences and rectal contrast agents. Examination *without* rectal filling has gained increasing popularity, since severe dysfunctions can be disclosed at maximal straining without the need of an evacuation phase (Vanbeckevoort et al. 1999, Bertschinger et al. 2002). As such, attempts to strain can be repeated several times to optimize capture of structural abnormalities (e.g. rectocoele) (Maccioni 2013). Only recently, a panel of experts from the European Society of Urogenital Radiology (ESUR) and the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) convened to define the minimum prerequisites to obtain a state-of-the-art MR examination of the pelvic floor (El Sayed et al. 2017). One of the key points was that static, dynamic and evacuation sequences should be generally performed. However, since all panellists were using MR with a conventional closed-magnet, procedural and technical aspects of pelvic floor imaging was focused to this type of system.

3.4. Objectives

3.4.1. Primary objectives

a. In patients and healthy volunteers (HV), to determine the rates (diagnostic yield) of structural abnormalities diagnosed by defaecography, with a focus on intussusception and rectocoele.

b. In patients and HV, to determine the rates (diagnostic yield) of functional abnormalities diagnosed by defaecography, with a focus on dyssynergic defaecation.

3.4.2. Secondary objectives

a. In patients, to determine whether differences exist in rates of main diagnosis between X-ray barium (BD) and magnetic resonance imaging defaecography (MRID).

b. In patients, to determine the rates (diagnostic yield) of structural abnormalities diagnosed by defaecography when rigid normative data ranges are applied as cut offs.

3.5. Methods

The authors developed the protocol for review, detailing pre-specified methods of analysis and eligibility of the studies in line with 2009 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidance (Liberati et al. 2009).

3.5.1. Study characteristics

Search term definitions were inclusive, promoting a wide search of studies reporting diagnostic yield of BD and/or MRID in patients with CC and/or HV. As the definition of

CC is not standardized and uniformly applied (Cook et al. 2009), all common terms encompassing problematic defaecation were used (Table 3.1).

Studies were eligible regardless of whether they were retrospective or prospective in design, controlled or uncontrolled. They were eligible if they provided extractable data on the prevalence of radiological abnormalities (structural and/or functional) on BD and/or MRID. Studies were ineligible for inclusion if they described the use of defaecography in patients suffering from bowel complaints other than constipation (e.g. faecal incontinence), and in whom constipation did not represent the primary presenting complaint. Similarly, studies were excluded if outcomes could not be segregated for the index population (i.e. coexistent constipation and faecal incontinence or anal pain, or gynaecologic complaints in women, where data were not stratified) and if the population affected by CC was enriched *a priori* based on clinical and/or radiological confirmation of specific abnormalities (either structural or functional). Studies without clear definition of radiological abnormalities were also excluded (i.e. definitions were neither reported in the text nor referenced in the methods).

A minimum population sample of 40 adult subjects (index population) was imposed for eligibility. This pragmatic threshold was taken to exclude case reports and small case series that often reported on early experience with the techniques.

TABLE 3.1 - SEARCH STRATEGY

Population terms
“constipation”[All Fields] OR "obstructed defaecation"[All Fields] OR "colonic inertia"[All Fields] OR "intussusception"[All Fields] OR "rectal prolapse"[All Fields] OR “outlet obstruction”[All fields] OR "SRUS"[All Fields] OR "solitary rectal"[All Fields] OR "defaecation disorder*"[All Fields]) OR “impaired defaecation”[All Fields] OR “rectal emptying”[All Fields] OR “bowel dysfunction*”[All Fields] OR “bowel function*”[All Fields] OR “evacuation difficulty*”[All Fields] OR “evacuation disorder*”[All Fields]
AND
“proctography”[All Fields] OR “proctographic”[All Fields] OR “proctogram”[All Fields] OR “defaecography”[All Fields] OR “defaecographic”[All Fields] OR “videoproctography”[All Fields] OR “videodefaecography”[All Fields] OR “cineproctography”[All Fields] OR “cinedefaecography”[All Fields]

3.5.2. Report characteristics

Any publication date was eligible to the date of the final search performed on 05 November 2017. Due to the large number of studies retrieved, it was decided to include only studies with full-text in the English language. This approach is supported by the evidence that literature searches limited to English language publications do not affect the quality of systematic reviews (Moher et al. 2003).

Only peer-reviewed publications reporting primary data were eligible. Thus reviews, editorials, and letters were excluded at the screening stage. Conference abstracts and proceedings were also excluded.

3.5.3. Information sources and study selection

The authors performed a comprehensive search of the literature using Medline (PubMed) and EMBASE and hand-searching using all common search terms encompassing problematic defaecation (Knowles et al. 2017) and defaecography with synonymous variants (Table 3.1). Reference lists of all full-texts were hand-selected for any additional studies.

3.5.4. Data extraction

Screening was performed at the abstract level by the junior authors (UG and HH), excluding studies not meeting eligibility criteria where these could be readily determined from the abstract alone. Full-text copies of all remaining studies were also obtained and assessed by the junior authors, who were un-blinded to the names of studies, authors, institutions or publications. Disagreement regarding inclusion was resolved by a senior author (SMS). Study characteristics and outcome data were extracted independently by the junior authorship team onto a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, Washington, USA), with disagreements resolved by consensus.

The following data were extracted for each study: publication year, country of origin, reason for exclusion, total number of patients, number of females, number of patients with constipation as primary complaint, number of HV, number of controls, mean or median age, bowel preparation prior to start the procedure, volumes of rectal, oral, vaginal, and/or vesical contrast, definitions and prevalence of structural (i.e. internal [stratified as recto-rectal and recto-anal where applicable] and external rectal prolapse, rectocoele [total and >4 cm], enterocoele, megarectum, dynamic perineal descent and

cut-off used for definition) and functional abnormalities (i.e. a) paradoxical or incomplete relaxation of the puborectalis muscle, b) incomplete opening of the anal canal, and/or c) incomplete rectal evacuation), and study quality using the component 1 (10-criterion checklist) proposed by Guo et al. (2016) to indicate the extent to which a case series presented traditional features of a statistical hypothesis-testing paradigm (Figure 3.1).

3.5.5. Meta-analysis and subgroup analyses

The proportion of structural and functional abnormalities in each study was combined to give a pooled prevalence for all studies. For structural abnormalities, this was performed irrespective of the criteria used to define their presence. However, calculation of pooled prevalence was made according to specific diagnostic criteria for pathologically significant intussusception and rectocoele (i.e. a magnitude not seen in studies in HV). Quantitative heterogeneity between studies was assessed using the I^2 statistic, acknowledging that the use of a specific threshold might lead to potentially misleading interpretation. Both fixed and random models results were presented, providing comments on the random effects when the I^2 was higher than 50% (commonly referred to as substantial heterogeneity) (Higgins 2011).

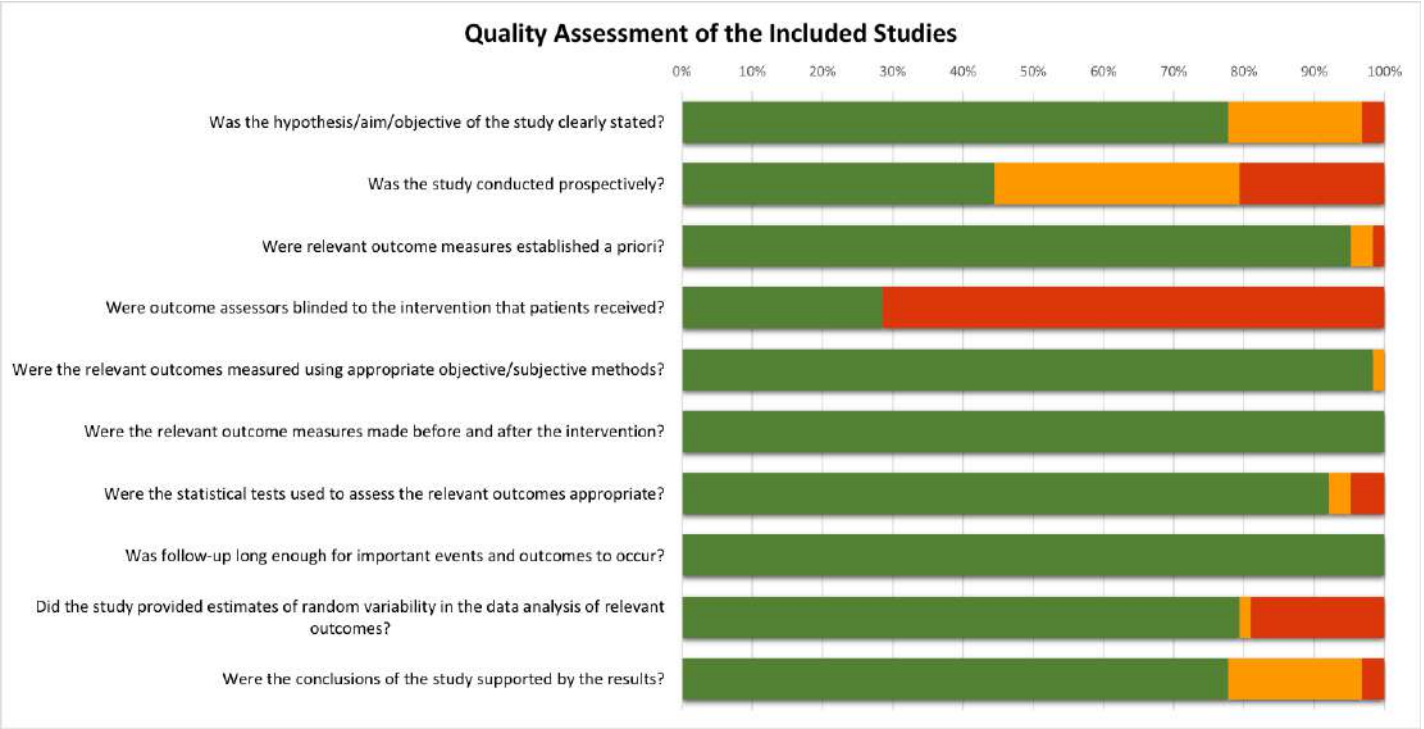


FIGURE 3.1 - COMPONENT 1 (10-CRITERION CHECKLIST) FOR QUALITY ASSESSMENT OF STUDIES.

KEY: GREEN = YES; ORANGE = PARTIAL OR UNCLEAR; RED = NO.

Subgroup analyses were conducted according to volume of rectal contrast administered (i.e. ≤150 ml, 151-200 ml, and >200 ml or defaecatory desire volume) and diagnostic criteria for functional abnormalities (see Data extraction). The prevalence of enterocoele was compared according to use of oral contrast using an odds ratio (OR) with a 95% confidence interval (CI). Comparisons between BD and MRID were performed using Freeman-Tukey double arcsine transformation. All data were pooled using fixed- and random-effects models with prevalence results reported along with 95%CI by the Wilson method. All analyses were performed in STATA 15 (StataCorp LLC, College Station, TX, USA), using the *Metaprop* function to obtain the pooled prevalence (Nyaga et al. 2014).

3.6. Summary of search results and study quality

3.6.1. Study selection

From a total of 1760 records identified, 1757 were screened after duplicates removed, 1582 of which were excluded. The database search yielded a total of 175 articles for full text review (Figure 3.2).

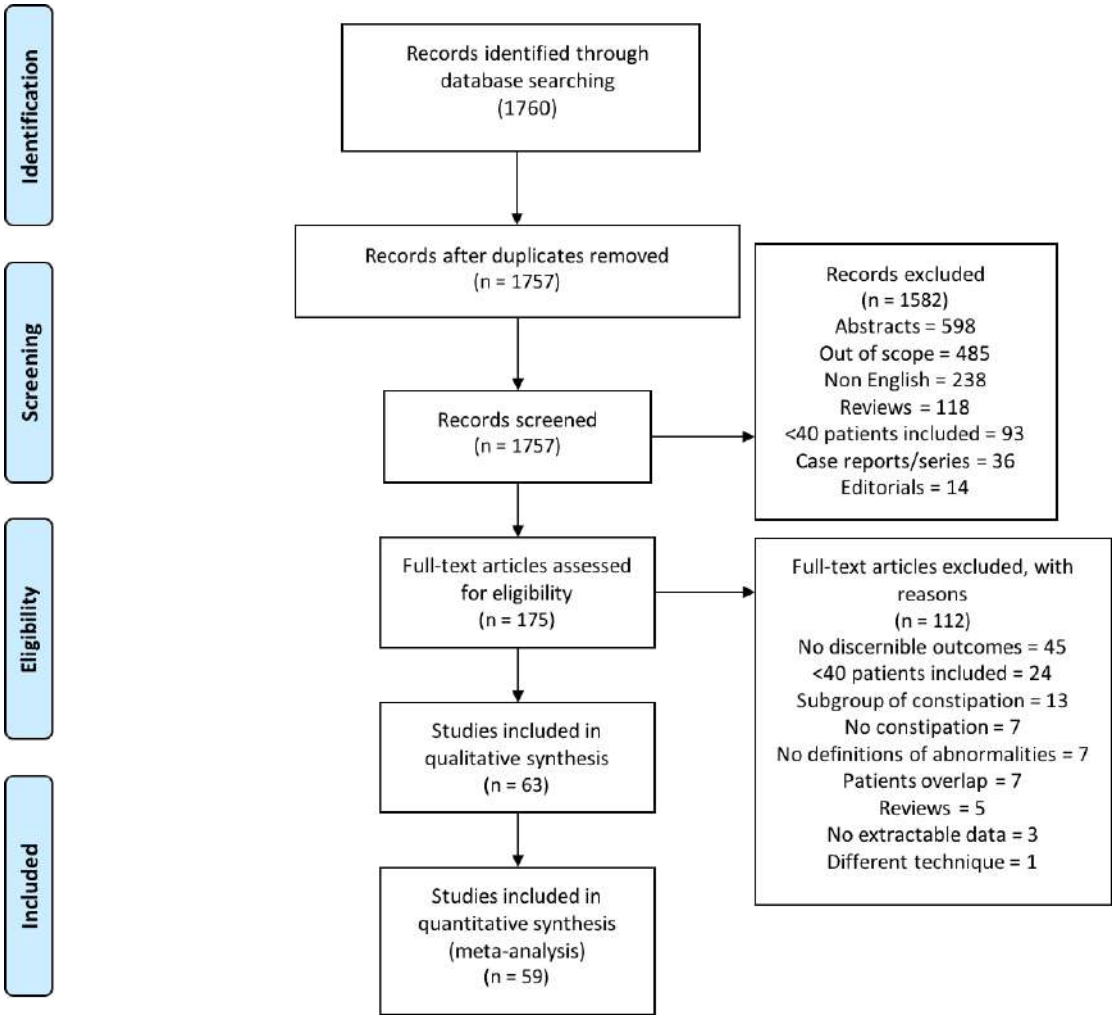


FIGURE 3.2 - PRISMA DIAGRAM.

Specific exclusions after full-text review included 45 studies where prevalence of radiological abnormalities in patients with CC could not be segregated from those suffering from other defaecatory disorders (faecal incontinence, anal pain, gynaecologic complaints in women); 24 studies where the population affected by CC was confirmed to be less than 40 patients; 13 studies where the population affected by CC was selected *a priori* based on clinical and/or radiological confirmation of specific abnormalities; 7 studies where CC did not represent the primary presenting complaint; 7 studies with no clear definition of radiological abnormalities; 7 publications reporting a patient cohort

that overlapped with other studies; 5 reviews; 3 studies with no extractable data on the prevalence of radiological abnormalities; 1 study where peritoneography was performed prior to defaecography.

Overall, 63 studies published between 1984 and 2017 contributed to the systematic review, providing data on the diagnostic yield of 7,519 BDs (range, 40-896 per study) and 668 MRIDs (range, 40-188 per study) in patients with CC, and 225 BDs (range, 8 to 47 per study) and 50 MRIDs (n = 1 study) in HV (Table 3.2). Overall, only 9 (14%) studies were controlled using either healthy (n = 2) (Dailianas et al. 2000, Brusciano et al. 2009) or non-healthy (n = 3; e.g. patients presenting for investigation of other complaints) volunteers (Wiersma et al. 1997, Tsiaoussis et al. 1998, Karlbom et al. 1999), or a combination of both subjects (n = 4) (Bartolo et al. 1988, Schouten et al. 1997, Faucheron and Dubreuil 2000, Gosselink et al. 2001).

Of the 63 articles included, 53 observational studies reported on BD, 5 on MRID, and 5 on direct comparisons between the two techniques. A total of 45 studies originated from European centres, 9 from the USA and 9 from other countries.

A total of 4 studies were conducted in HV and 59 studies in patients with CC. Of these, 50 reported on the prevalence of structural and/or functional abnormalities using BD, 4 using MRID, and 5 using both techniques (comparative studies).

A total of 60/63 (95%) studies reported a male/female ratio. Of these, only 1 study exclusively recruited male patients with CC (Viscardi et al. 2012). The other 59 studies reported outcomes on 6,334 (87%; median 72, interquartile range [IQR] 52-113) females and 931 (median 12, IQR 0-22) males among CC patients (n=55 studies), and 110 (55%; median 27, IQR 24-33) females and 89 (median 23, IQR 19-25) males among HV (n=4 studies).

TABLE 3.2 - ALL STUDIES INCLUDED IN THE SYSTEMATIC REVIEW.

Author	Year	Country	Technique	Patients* (N)	Controls (N)
Mahieu	1984	Belgium	BD	0	56†
Mahieu	1984	Belgium	BD	144	0
Bartolo	1988	UK	BD	49	25§
Shorvon	1989	Canada	BD	0	47
Felt-Bersma	1990	The Netherlands	BD	43	0
Poon	1991	UK	BD	63	0
Nielsen	1993	Denmark	BD	93	0
Siproudhis	1993	France	BD	50	0
Ger	1993	USA	BD	116	0
Klauser	1994	Germany	BD	97	0
Lee	1994	Taiwan	BD	55	0
Karlbom	1995	Sweden	BD	80	0
Halligan	1995	UK	BD	74	0
Halligan	1996	UK	BD	60	0
Agachan	1996	USA	BD	232	0
Schouten	1997	The Netherlands	BD	170	29§
Wiersma	1997	The Netherlands	BD	248	14†
Pfeifer	1997	USA	BD	100	0
Tsiaoussis	1998	Greece	BD	162	44†
Glia	1998	Sweden	BD	134	0
Mellgren	1998	Sweden	BD	112	0
Karlbom	1999	Sweden	BD	215	30†
Spazzafumo	1999	Italy	BD	316	0
Barthet	2000	France	BD	43	0
Faucheron	2000	France	BD	154	25§
Goh	2000	UK	MRID	0	50
Dailianas	2000	Greece	BD	49	22
Stojkovic	2000	UK	BD	136	0
Mibu	2001	Japan	BD	46	0
Gosselink	2001	The Netherlands	BD	80	60§
Savoye-Collet	2003	France	BD	52	0
Yeh	2003	USA	BD	261	0
Karlbom	2004	Sweden	BD	127	0
Dvorkin	2005	UK	BD	896	0
Renzi	2006	Italy	BD	420	0
Soares	2009	Brazil	BD	45	0
Brusciano	2009	Italy	BD	84	10
Murad-Regadas	2009	USA	BD	255	0

Morandi	2010	Italy	BD	567	0
Baek	2010	South Korea	BD	136	0
Mohammed	2010	UK	BD	200	0
Vitton	2011	France	C	56	0
Martellucci	2011	Italy	BD	54	0
Regadas	2011	*Multicentre*	BD	86	0
Ribas	2011	Spain	BD	106	0
Bordeianou	2011	USA	BD	123	0
Viscardi	2012	Italy	BD	46	0
Pilkington	2012	UK	C	42	0
Alves-Ferreira	2012	USA	BD	58	0
Piloni	2013	Italy	MRID	105	0
Seong	2013	South Korea	BD	96	0
Adusumilli	2013	UK	BD	64	0
Kashyap	2013	USA	BD	45	0
Andrade	2014	Portugal	BD	300	0
Palit	2014	UK	BD	0	46
Li	2015	China	MRID	56	0
Heinrich	2015	Switzerland	MRID	188	0
Kassis	2015	USA	BD	61	0
Hassan	2016	Egypt	MRID	76	0
Palit	2016	UK	BD	100	0
Zafar	2017	UK	C	55	0
Poncelet	2017	France	C	50	0
Martín-Martín	2017	Spain	C	40	0

**Patient suffering from chronic constipation (NB: the number may differ from the original total sample size). BD: barium defaecography; MRID: magnetic resonance imaging defaecography; C: studies comparing BD vs. MRID; [†]Non-healthy controls; [§] Combination of non-healthy and healthy controls.*

3.6.2. Study quality

The 63 included studies were all observational with no experimental allocation to tests. The majority of studies were retrospective in nature (56%). One further limitation was blinding, with only 28% of studies stating that all defaecographic images were reviewed by assessors who were not aware of the patient history to minimize observer bias (Figure 3.1). Duration of follow-up was reported in 17/28 (61%) prospective studies with a mean (standard deviation) of 23 (14) months of follow-up. Interestingly, prevalence of

the 2 most common truly pathological structural abnormalities (i.e. recto-anal intussusception and large [>4 cm] rectocoele – discussed in detail below) was higher in prospective than retrospective studies (33.7 [21.0-47.6] vs. 17.1 [10.6-24.7], and 23.1 [14.5-32.9] vs. 11.6 [5.6-19.2], respectively).

3.6.3. Structural abnormalities

3.6.3.1. Patients

3.6.3.1.1. Intussusception

Pooled prevalence of intussusception on BD was 36.8% (95%CI, 31.7-42.0) (Table 3.3) in patients with CC, and affected up to one third of patients with a clinically confirmed rectocoele (Figure 3.3) (Thompson et al. 2002).

TABLE 3.3 - DEFINITIONS AND POOLED PREVALENCE OF STRUCTURAL ABNORMALITIES ON X-RAY BARIUM (BD) AND MAGNETIC RESONANCE IMAGING DEFAECOGRAPHY (MRID) IN HEALTH AND CONSTIPATION.

Structural abnormalities		Health		Constipation			
		Overall % (95%CI)	N studies	Overall % (95%CI)	N studies	Pathological* % (95%CI)	N studies
BD	*Intussusception*	20-70 (NA)†	2	36.8 (31.7-42.0)	46	23.7 (16.8-31.4)††	13
	External prolapse	0 (NA)	2	5.3 (3.1-8.0)	16	5.3 (3.1-8.0)	16
	Rectocoele	81-100 (NA)§	2	54.1 (48.0-60.2)	44	15.9 (10.4-22.2)§§	9
	Enterocoele	0 (NA)	2	16.8 (12.7-21.4)	27	16.8 (12.7-21.4)	27
	Perineal descent	0 (NA)	2	44.4 (36.2-52.7)	18	44.4 (36.2-52.7)	18
MRID	*Intussusception*	0 (NA)	1	34.5 (21.9-48.3)	9	42.4 (34.0-51.0)††	3
	External prolapse	0 (NA)	1	4.6 (0.0-19.5)	3	4.6 (0.0-19.5)	3
	Rectocoele	0 (NA)	1	64.6 (50.8-77.4)	9	14.5 (0.0-45.8)§§	3
	Enterocoele	0 (NA)	1	15.8 (7.6-26.1)	8	15.8 (7.6-26.1)	8
	Perineal descent	6 (NA)	1	43.6 (26.6-61.3)	4	43.6 (26.6-61.3)	4

** Not seen in health; CI: confidence interval; NA: not applicable*

† Oxford I or II (i.e. recto-rectal intussusception)

†† Oxford III or IV (i.e. recto-anal intussusception)

§ <4 cm depth observed in females compared to 0-13% in males (43-56% overall)

§§ >4 cm depth.

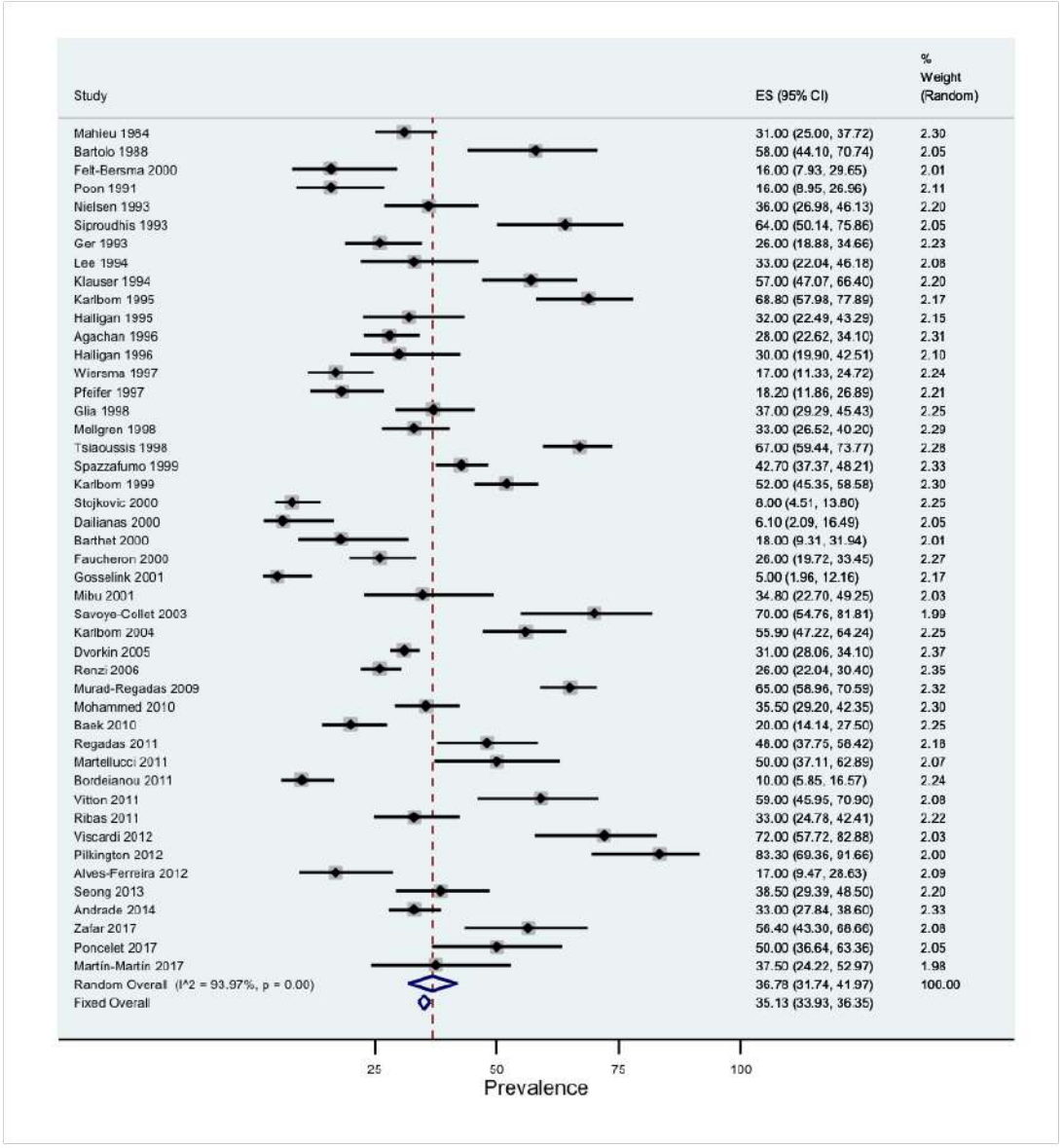


FIGURE 3.3 - FOREST PLOT SHOWING RATES OF INTUSSUSCEPTION ON X-RAY BARIUM DEFAECOGRAPHY (PERCENTAGE OF PATIENTS).

Similar rates of intussusception were observed on MRID (34.5 [21.9-48.3; based on 9 studies]) (Figure 3.4).

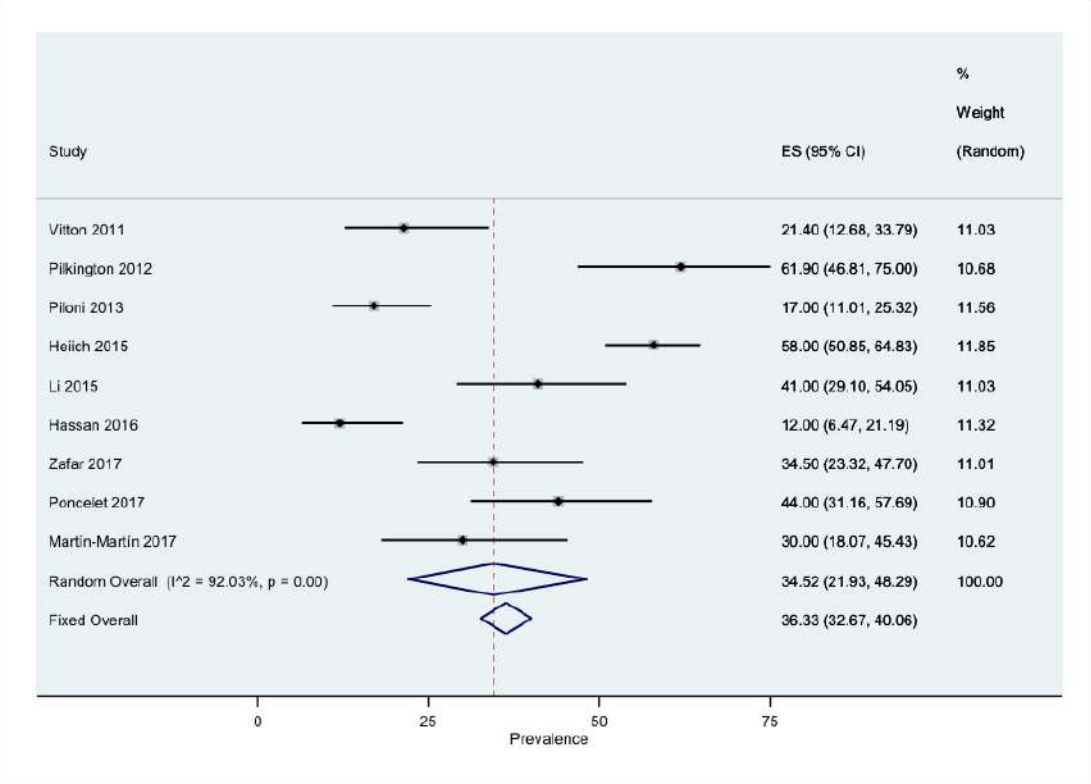


FIGURE 3.4 - FOREST PLOT SHOWING RATES OF INTUSSUSCEPTION ON MAGNETIC RESONANCE IMAGING DEFAECOGRAPHY (PERCENTAGE OF PATIENTS).

The definition of intussusception was reported and/or referenced in a total of 40/63 (63%) studies. Among these, 3 main grading systems were used to define the severity of intussusception, originally described as “unilateral or circumferential infolding of the rectum during straining” (Mahieu et al. 1984). A total of 7 studies (Shorvon et al. 1989, Siproudhis et al. 1993, Karlbom et al. 2004, Mohammed et al. 2010, Viscardi et al. 2012, Palit et al. 2014, Palit et al. 2016) adopted the classification proposed by Shorvon et al. (1989), which identifies 7 degrees of intussusception, with grades 1 to 4 inclusive being intra-rectal (1 and 2: <3 mm; unilateral or circumferential, respectively; 3 and 4: >3 mm;

unilateral or circumferential, respectively), 5 and 6 intra-anal (the leading edge of the infolding impinges onto or into the anal canal, respectively), and 7 representing an external rectal prolapse.

Among the 40 studies reporting definitions of intussusception, a total of 24 recognized intussuscepta as either unilateral or circumferential, whereas 16 studies regarded only circumferential intussuscepta as a truly abnormal finding. Among the former group, only 6 studies utilized specific cut-offs to determine the significance of the infolding: any fold "more than a wrinkling of the mucosa" (n=1) (Klauser et al. 1994), ≥3 mm (n=1) (Dvorkin et al. 2005), >4 mm (n=2) (Agachan et al. 1996, Ribas et al. 2011), or >1 cm (n=2) (Spazzafumo and Piloni 1999, Renzi et al. 2006). When only reported if circumferential, intussuscepta were broadly stratified into intra-rectal, intra-anal, and external rectal prolapse, as originally described by Karlbom et al. (1995). Only 1 study adopted the more recent Oxford Prolapse Grade system (Adusumilli et al. 2013) to recognise intussuscepta, with the leading edge of the infolding descending no lower than proximal limit of the rectocoele (grade I), or into the level of the rectocoele but not onto sphincter/anal canal (grade II), or onto sphincter/anal canal (grade III), or into sphincter/anal canal (grade IV), or protruding from the anus (grade V) (Figure 3.5).

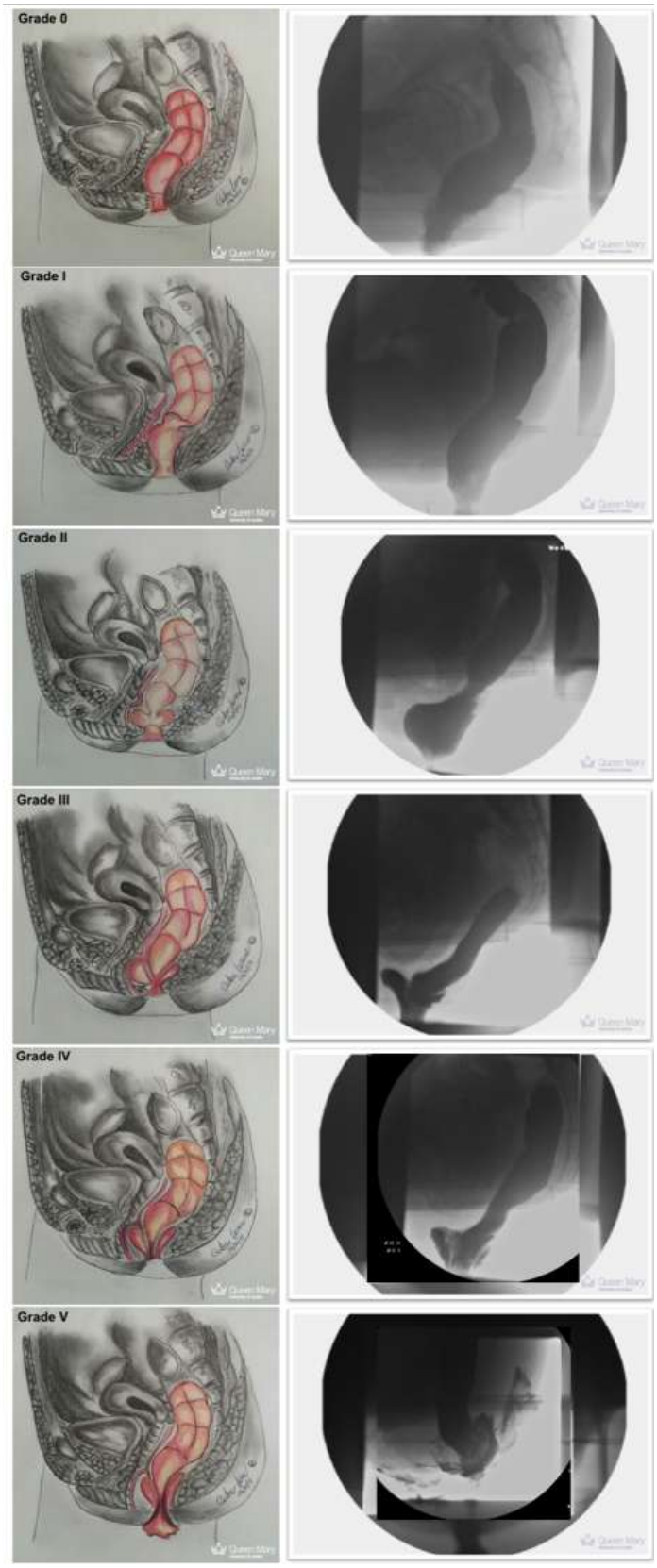


FIGURE 3.5 - OXFORD GRADING SYSTEM FOR RECTAL PROLAPSE.

3.6.3.1.2. Rectocoele

Pooled prevalence of a rectocoele on BD was 54.1% (95%CI, 48.0-60.2) in patients with CC (Figure 3.6).

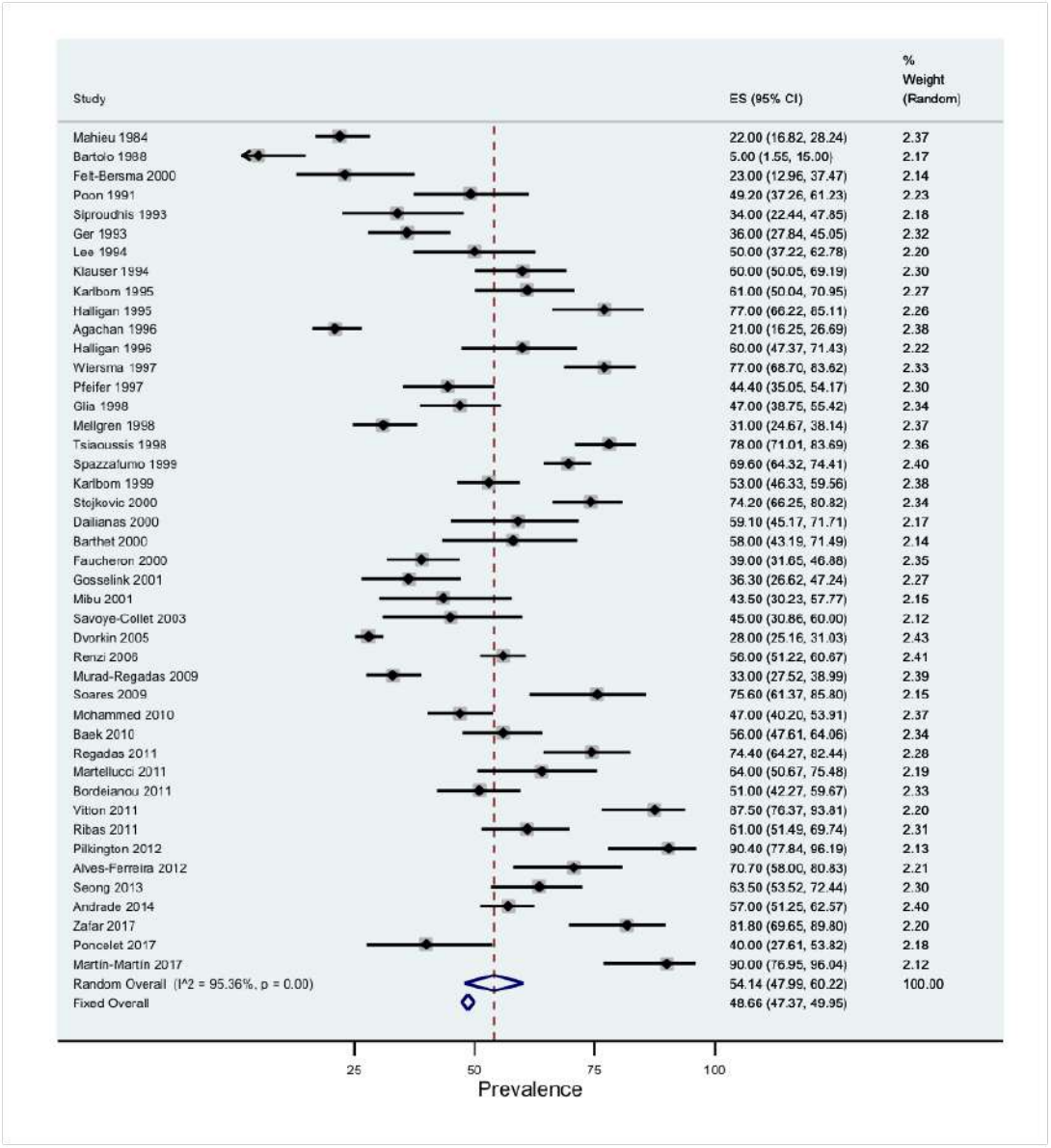


FIGURE 3.6 - FOREST PLOT SHOWING RATES OF RECTOCOELE ON X-RAY BARIUM DEFAECOGRAPHY (PERCENTAGE OF PATIENTS).

The definition of rectocoele was reported and/or referenced in a total of 41/63 (65%) studies. Rectocoele has traditionally been defined as an outpouching of the rectal wall on defaecation (Mahieu et al. 1984). A total of 17/41 studies defined a cut-off of

rectocoele depth to establish the diagnosis: 2 cm (n=9) (Goh et al. 2000, Dvorkin et al. 2005, Murad-Regadas et al. 2009, Baek et al. 2010, Vitton et al. 2011, Piloni et al. 2013, Li et al. 2015, Hassan et al. 2016, Martin-Martin et al. 2017); 2.5 cm (n=1) (Poncelet et al. 2017); 3 cm (n=4) (Siproudhis et al. 1993, Agachan et al. 1996, Faucheron and Dubreuil 2000, Savoye-Collet et al. 2003); or 4 cm (n=3) (Nielsen et al. 1993, Kashyap et al. 2013, Palit et al. 2016). However, the approach adopted to calculate rectocoele size during maximum straining has been detailed in only 9 of these as: a) the 'maximum depth of the bulge beyond the expected and extrapolated line of the anterior rectal wall' (n=2) (Shorvon et al. 1989, Vitton et al. 2011), or the 'distance between the maximal anterior outbulge and b) the axis of the anal canal' (n=2) (Halligan et al. 1995, Karlbom et al. 1995), or c) 'a line through aspect of anorectal junction' (n=1) (Piloni et al. 2013) or 'a line drawn parallel to the centre of the anal canal during straining' (n=2) (Li et al. 2015, Hassan et al. 2016), or d) 'outpouching of the anterior rectal wall ahead of rectovaginal septum, persisting on incomplete evacuation' (n=2) (Savoye-Collet et al. 2003, Murad-Regadas et al. 2009).

The amount of contrast retained within the rectocoele has been reported as a measure of clinical significance in only 9/41 studies (Glia et al. 1998, Dvorkin et al. 2005, Murad-Regadas et al. 2009, Baek et al. 2010, Mohammed et al. 2010, Andrade et al. 2014, Palit et al. 2014, Palit et al. 2016, Poncelet et al. 2017).

3.6.3.1.3. Enterocoele

Among the 27/59 (46%) studies reporting its prevalence in CC, enterocoele affected a larger proportion of patients in studies describing the use of oral contrast (n=11) compared to those that did not (n=16) (20.4% [95%CI, 15.6-25.6] vs. 14.4% [8.8-21.1%],

respectively; odds ratio [OR], 1.18 [1.08-1.30], p=0.0007), with an overall prevalence of 16.8% (95% CI, 12.7-21.4) on BD and 15.8% (95% CI, 7.6-26.1) on MRID (Figure 3.7).

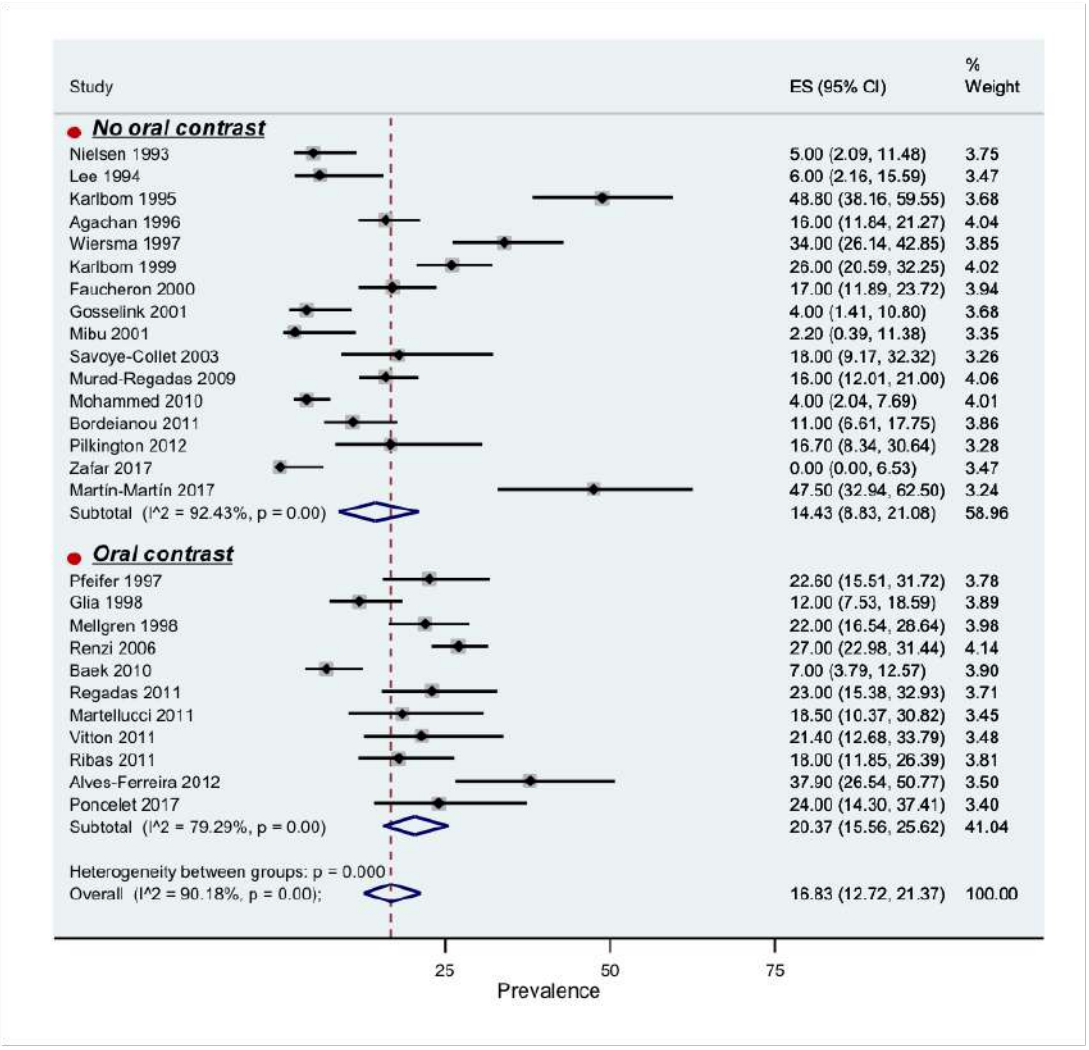


FIGURE 3.7 - FOREST PLOT SHOWING RATES OF ENTEROCOELE ON X-RAY BARIUM DEFAECOGRAPHY IN STUDIES WITH OR WITHOUT THE USE OF ORAL CONTRAST (PERCENTAGE OF PATIENTS). KEY: ES= EFFECT SIZE; CI = CONFIDENCE INTERVAL.

Enterocoele has traditionally been defined as a herniation of the posterior *cul-de-sac* downward between the vagina and rectum (Maglinte et al. 1997). The hernia may contain small bowel or sigmoid colon. In the latter case, it is more commonly defined 'sigmoidocoele'. Since Shorvon description of enterocoele as an 'indentation of

posterior vaginal wall and anterior rectal wall' (Shorvon et al. 1989), various defaecographic definitions have been provided, with the simplest including 'external compression of the anterior rectal wall during straining' (Lee et al. 1994), or 'contrast filled loops between rectum and vagina in women, and anterior to the rectum in men' (Karlbom et al. 1999), or 'semilunar defect in rectum during straining' (Mibu et al. 2001). Studies using MRID provide more accurate definitions, such as 'small bowel within the rectovaginal septum that reached or crossed the junction of the upper one third and distal two thirds of the vagina' , or 'herniation of the peritoneal sac into the rectogenital space below the pubococcygeal line' (Li et al. 2015). A definition of enterocoele and/or sigmoidocoele was provided in only 22/63 (35%) studies. Small bowel opacification is pivotal to making a definitive diagnosis of enterocoele with standard BD, otherwise it is difficult to determine whether a widened rectovaginal space is due to a herniated mesentery or a prolapsed uterus, rather than enterocoele (Maglinte et al. 1997). However, administration of oral contrast was reported in only 19/63 (30%) studies.

3.6.3.1.4. Perineal descent

Descending perineum syndrome was first defined by Parks et al. (1966) as an excessive ballooning of the perineum below the bony outlet of the pelvis associated with symptoms of ED, rectal pain, mucus discharge and/or rectal bleeding. Although measurement of perineal descent has been extensively reported in studies, there is poor consensus on definitions and pathophysiological implications. Lack of standardization comes from which position of the perineum should be measured, whether at rest (static) or during straining (dynamic). Even for the latter, various cut-off values have been used, ranging from 2 to 6 cm (Felt-Bersma et al. 1990, Renzi et al. 2006), making estimate and

comparison of prevalence rates very difficult (Table 3.4). Also, anatomical/fixed reference points vary among studies and include: pubococcygeal line (Mahieu et al. 1984); upper surface of the commode (Halligan et al. 1995); ischial tuberosity (Karlbom et al. 1995); a water-filled ring (Felt-Bersma et al. 1990).

TABLE 3.4 - DEFINITIONS AND PREVALENCE OF DYNAMIC PERINEAL DESCENT ON BARIUM DEFAECOGRAPHY (BD).

Cut off (cm)	No. studies*	No. BD	Reference point from ARJ on straining	Pooled prevalence (%, 95%CI)	I^2 (%), *p* value
2	2	99	PCL (Vitton et al. 2011); Water-filled ring (Felt-Bersma et al. 1990)	54.3 (44.3-64.1)	NA
3	7	884	PCL (Poon et al. 1991, Lee et al. 1994, Agachan et al. 1996, Glia et al. 1998, Barthet et al. 2000); ARJ at rest (Savoye-Collet et al. 2003); IT (Spazzafumo and Piloni 1999)	40.5 (25.2-56.8)	95.3, <0.001
3.5	5	1,009	PCL (Alves-Ferreira et al. 2012, Andrade et al. 2014); ARJ at rest (Morandi et al. 2010, Martin-Martin et al. 2017); IT (Martellucci and Naldini 2011)	43.2 (28.6-58.4)	94.1, <0.001
4	3	411	ARJ at rest and/or PCL (Siproudhis et al. 1993); PCL or other fixed landmarks (Ribas et al. 2011); ARJ at rest (Murad-Regadas et al. 2009)	44.6 (25.4-64.6)	92.7 <0.001
6	1	420	PCL (Renzi et al. 2006)	61.4 (NA)	NA

**Data available in only 18/59 (31%) studies; ARJ: anorectal junction; CI: confidence interval; PCL: pubococcygeal line; IT: ischial tuberosity; NA: not applicable.*

Pooled prevalence of significant dynamic perineal descent in patients with CC was 44.4% (95% CI, 36.2-52.7) on BD and 43.6 (26.6-61.3) on MRID (Figure 3.8).

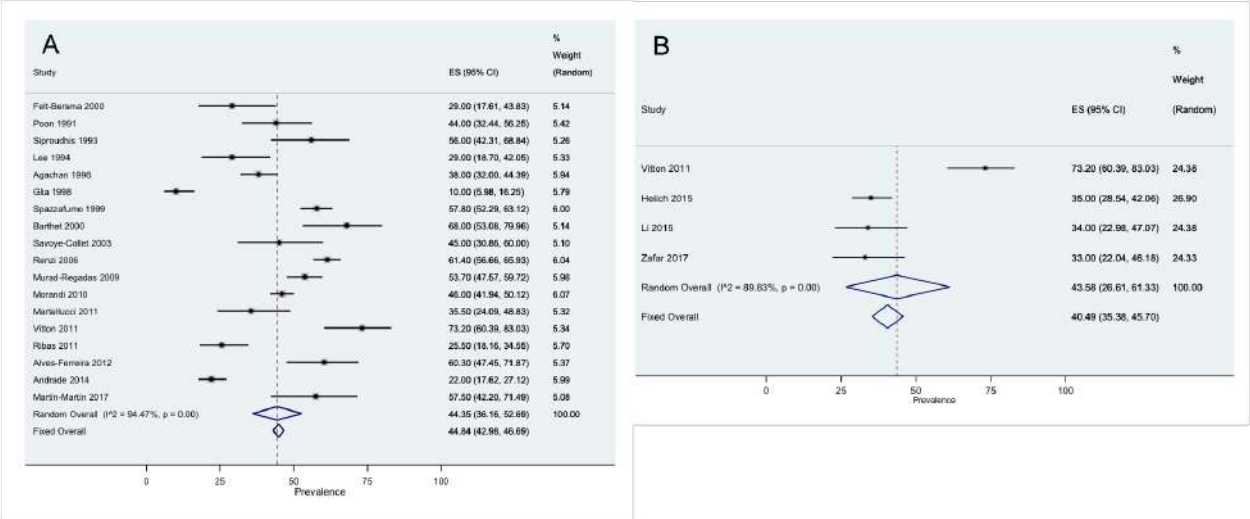


FIGURE 3.8 - FOREST PLOT SHOWING RATES OF PERINEAL DESCENT ON X-RAY BARIUM (A) AND MAGNETIC RESONANCE IMAGING (B) DEFAECOGRAPHY (PERCENTAGE OF PATIENTS).

3.6.3.1.5. Megarectum

Prevalence of megarectum (Gladman and Knowles 2008) in CC was reported in only 2 studies (Spazzafumo and Piloni 1999),(Mohammed et al. 2010). Based on findings of BD prospectively performed on 46 HV (28 women), Palit et al. (2014) suggested that a rectal diameter of >8.1 cm in men and >6.9 cm in women is indicative of megarectum. Using these parameters, Mohammed et al. (2010) found a megarectum in 7% (14/200) of constipated patients. Spazzafumo and Piloni (1999) regarded as abnormal an ampulla >7 cm in diameter on the lateral view, observing this finding in 31% of CC patients.

3.6.3.2. Healthy volunteers (HV)

In only 4 of the 12 controlled studies, the control group was entirely composed of truly HV (Voderholzer et al. 1997, Dailianas et al. 2000, Gladman et al. 2003, Brusciano et al. 2009). A total of 4 studies, 2 using BD (Shorvon et al. 1989, Palit et al. 2014) and 2 MRID (Goh et al. 2000, Tirumanisetty et al. 2018), provided normal data by exclusively including >40 subjects.

Despite adopting the same classification system and reporting on a similar gender ratio, the prevalence of intussusception in the study by Shorvon et al. (1989) was much higher than that reported by Palit et al. (2014) (70% vs 20%, respectively). Rectocoele has been much more frequently observed in female (81-100%) than male (0-13%) volunteers on BD (Shorvon et al. 1989, Palit et al. 2014).

Goh et al. (2000) used MRID to characterize 50 HV (25% females): whilst excessive anorectal junction descent (>3 cm below the pubococcygeal line on maximum strain) was observed in 6% of subjects, prevalence of intussusception, rectocoele and enterocoele was 0%.

As noted previously, the overlap in presence of structural abnormalities between health and disease is a frequently cited limitation of defaecography (Faucheron et al. 2018). Accordingly, grade or severity of abnormality should be considered, and what reflects the pathology (discussed in detail below). Palit et al. (2014) proposed that only recto-anal (not recto-rectal) intussusceptions and rectocoeles of ≥4.0 cm depth should be considered as truly abnormal findings on BD with regard to size, although it is acknowledged that smaller rectocoeles may be clinically relevant in some patients.

Among HV, prevalence of enterocoele is rare, ranging from 0% on MRID (Goh et al. 2000) to only 4% on BD (Shorvon et al. 1989). Extension of the small bowel up to 2 cm below the vaginal apex has been considered as within the normal range (Maglinte et al. 1997).

3.6.4. Significant structural abnormalities in constipated patients

Prevalence of recto-anal (i.e. Oxford III and IV) intussusception (Figure 3.9) and external rectal prolapse (i.e. Oxford V) on BD is 23.7% (95%CI, 16.8-31.4; based on 13 studies) and 5.3% (3.1-8.0; based on 16 studies), respectively. When considering large (>4 cm) rectocoele only, the prevalence, based on 9 studies, is 15.9% (95%CI, 10.4-22.2) (Figure 3.9).

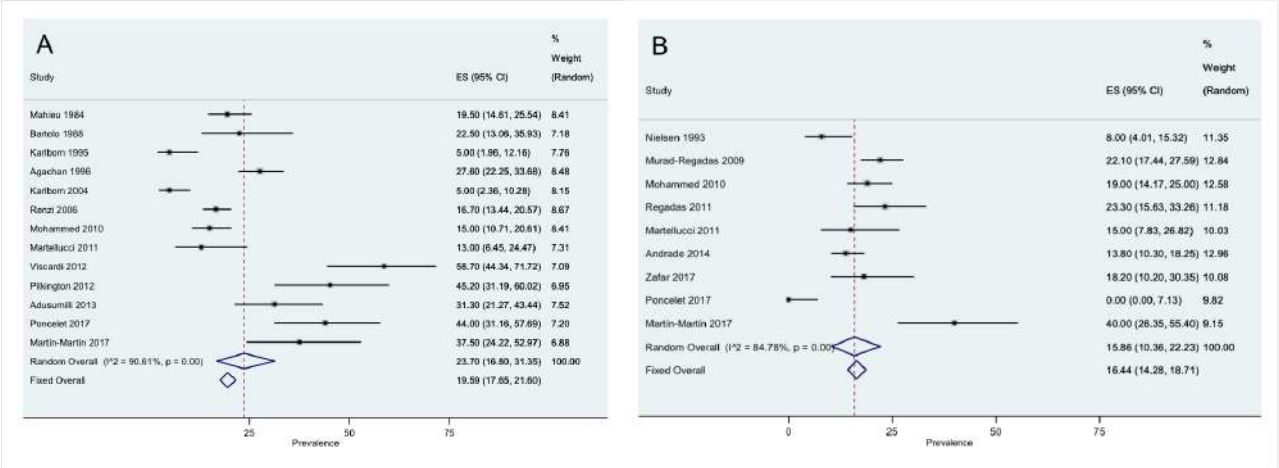


FIGURE 3.9 - FOREST PLOT SHOWING RATES OF STRUCTURALLY SIGNIFICANT INTUSSUSCEPTION (OXFORD III AND IV; A) AND RECTOCOELE (≥4 CM DEPTH; B) ON X-RAY BARIUM DEFAECOGRAPHY (PERCENTAGE OF PATIENTS).

KEY: ES= EFFECT SIZE; CI = CONFIDENCE INTERVAL.

3.6.5. Functional abnormalities

3.6.5.1. Patients

On defaecography, the diagnosis of a functional abnormality is made using 3 possible features, either combined or isolated, originally described by Mahieu et al. (1984): a) poor opening of the anorectal angle (secondary to poor relaxation or indeed 'paradoxical' contraction of the puborectalis muscle); b) poor anal sphincter relaxation; c) incomplete and/or prolonged evacuation based on percentage of contrast expelled and/or time taken, respectively.

Among the 59 studies in patients with CC, diagnostic criteria and prevalence of functional abnormalities were provided in 42 (71%), based on either a) (n = 22) (Mahieu et al. 1984, Bartolo et al. 1988, Lee et al. 1994, Karlbom et al. 1995, Halligan and Bartram 1996, Schouten et al. 1997, Glia et al. 1998, Spazzafumo and Piloni 1999, Dailianas et al. 2000, Faucheron and Dubreuil 2000, Stojkovic et al. 2000, Gosselink et al. 2001, Brusciano et al. 2009, Murad-Regadas et al. 2009, Soares et al. 2009, Baek et al. 2010, Morandi et al. 2010, Bordeianou et al. 2011, Martellucci and Naldini 2011, Ribas et al. 2011, Andrade et al. 2014, Martin-Martin et al. 2017); b) (n = 2) (Ger et al. 1993, Siproudhis et al. 1993); c) (n = 2) (Kassis et al. 2015, Zafar et al. 2017); a+b) (n = 4) (Felt-Bersma et al. 1990, Nielsen et al. 1993, Karlbom et al. 1999, Poncelet et al. 2017); a+c) (n = 7) (Poon et al. 1991, Agachan et al. 1996, Barthet et al. 2000, Yeh et al. 2003, Alves-Ferreira et al. 2012, Pilkington et al. 2012, Viscardi et al. 2012); b+c) (n = 1) (Kashyap et al. 2013); or a+b+c) (n = 4) (Regadas et al. 2011, Seong and Kim 2013, Heinrich et al. 2015, Palit et al. 2016). Quantitative meta-analysis of these studies, including 4

comparative (BD vs. MRID) studies, showed a pooled prevalence of 24.1% (95% CI, 20.2-28.4) on BD and 25.9 (14.1-39.6) on MRID (Figure 3.10).

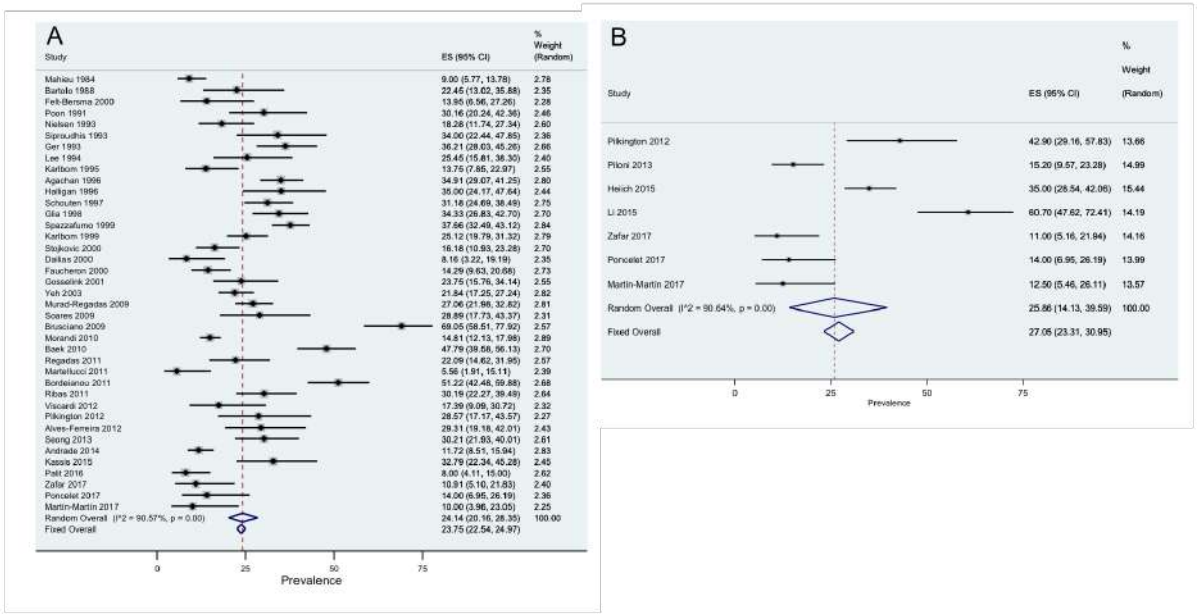


FIGURE 3.10 - FOREST PLOT SHOWING RATES OF FUNCTIONAL ABNORMALITIES ON X-RAY BARIUM (A) AND MAGNETIC RESONANCE IMAGING (B) DEFAECOGRAPHY (PERCENTAGE OF PATIENTS).

Prevalence of functional abnormalities in studies where diagnosis was based on the assessment of defaecatory dynamics in isolation, compared with those adding parameters of rectal emptying was near identical on BD (23.6% vs. 24.2%, respectively; OR 1.05 [0.93-1.19], p=0.454), but notably different on MRID (23.9% vs. 36.3%; OR 1.81 [95%CI,1.12-2.91], p=0.013). (Table 3.5).

TABLE 3.5 - PREVALENCE OF FUNCTIONAL ABNORMALITIES ON DEAFECOGRAPHY ACCORDING TO DIAGNOSTIC CRITERIA IN PATIENTS WITH ED.

Defaecography	Diagnostic criteria	No. studies	No. defaecographies	Pooled prevalence (%, 95%CI)	I^2 (%), *p* value	OR (95%CI), *p* value
BD	a±b	26	3,584	23.6 (18.4-29.2)	93.7, <0.001	1.05 (0.93-1.19), 0.454
	a±b+c	9	984	24.2 (18.2-30-8)	79.3, <0.001	
MRID	a±b	4	251	23.9 (6.7-47.1)	93.1, <0.001	1.81 (1.12-2.91), 0.013
	a±b+c	2	230	36.3 (30.2-42.7)	NA	

BD: barium defaecography; MRID: magnetic resonance imaging defaecography; a: poor opening of the anorectal angle (secondary to non-relaxation or contraction of puborectalis muscle); b: poor anal sphincter relaxation; c: incomplete and/or prolonged evacuation; CI: confidence interval; OR: odds ratio; NA: not applicable.

Table 3.6 describes the pooled prevalence in studies using either 50-150 ml vs. 151-200 ml vs. >200 ml of contrast, or defaecatory desire volume. The volume of rectal contrast used for BD did not influence the prevalence of functional abnormalities, which was slightly lower in studies using up to 150 ml compared with 151-200 ml of rectal contrast (22.0% vs. 27.2%). This finding was borderline statistically significant (OR, 0.85 [95%CI 0.71-1.01]; *p*=0.064).

TABLE 3.6 - PREVALENCE OF FUNCTIONAL ABNORMALITIES ON X-RAY BARIUM DEFAECOGRAPHY (BD) ACCORDING TO VOLUME OF RECTAL CONTRAST.

Rectal contrast (ml)	No. studies	No. BD	Pooled prevalence (%, 95%CI)	I^2 (%), *p* value
≤150	8	554	22.0 (15.9-28.7)	69.2, <0.001
151-200	9	1,726	27.2 (17.5-38.1)	95.4, <0.001
>200 or DDV	18	2,125	24.7 (19.0-30.8)	89.7, <0.001

CI: confidence interval; DDV: defaecatory desire volume.

3.6.5.2. Healthy volunteers (HV)

Mahieu et al. (1984) defined criteria for 'normality' based on 5 functional parameters in 56 subjects with no symptoms of ED (non-healthy controls): increased anorectal angulation, obliteration of the impression of the puborectalis muscle, wide opening of the anal canal, total evacuation of the rectal contents, and normal resistance of the pelvic floor. In a recent series of 113 asymptomatic women undergoing MRID (Tirumanisetty et al. 2018), median contrast (ultrasound gel) evacuation was 57%, with 20% proposed as the lower limit of the normal range; this perhaps is a reflection of the supine study position. The authors suggested that only patients who are unable to empty above this cut-off should be considered abnormal on MRID.

3.6.6. Normal findings in constipated patients

Pooled prevalence of normal findings on BD in CC was 16.7% (95%CI, 12.2-21.8) based on 19 studies incorporating a total of 3,086 investigations (Figure 3.11).

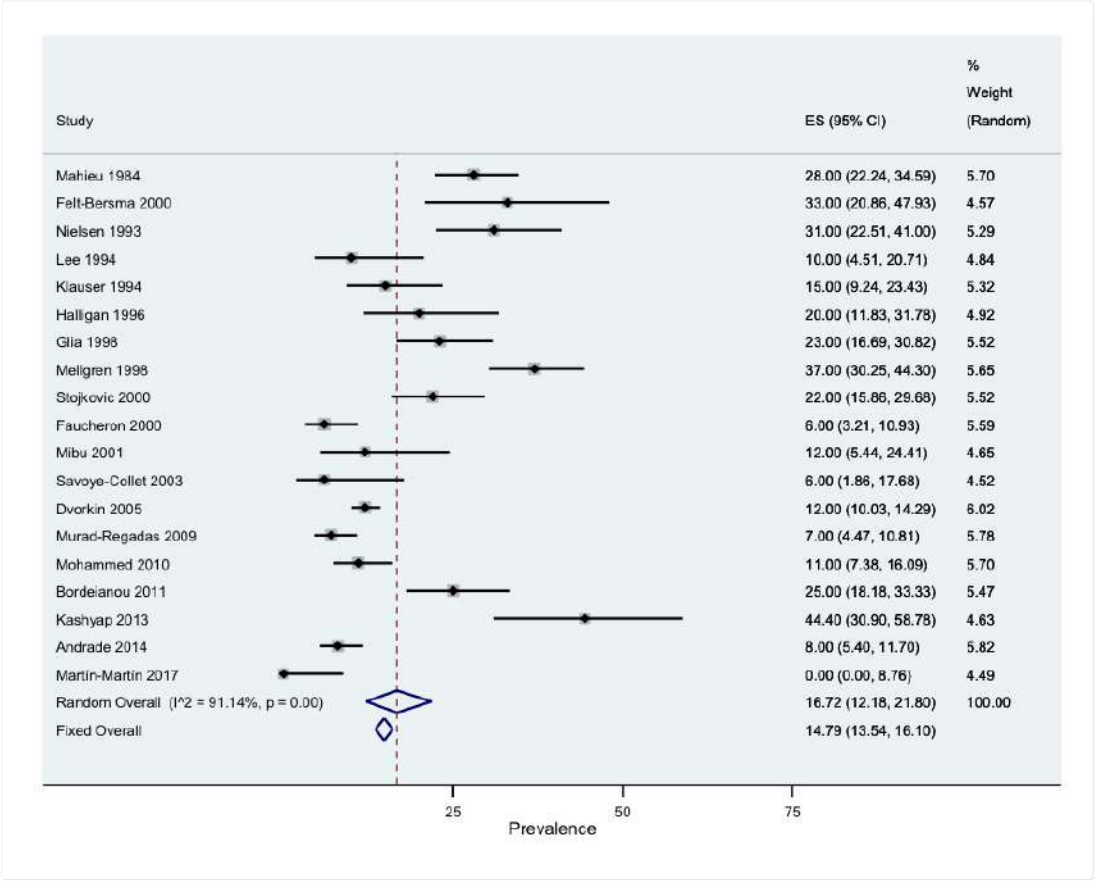


FIGURE 3.11 - FOREST PLOT SHOWING RATES OF NORMAL FINDINGS ON X-RAY BARIUM DEFAECOGRAPHY (PERCENTAGE OF PATIENTS).

3.6.7. Comparison of BD with MRID in constipated patients

A total of 5 studies compared BD with MRID. BD represented the reference standard in all studies, except one adopting the results obtained from the joint analysis of BD and MRID as reference (Poncelet et al. 2017). Vitton et al. (2011) compared the accuracy of dynamic anorectal endosonography and MRID with BD as the reference standard in the diagnosis of pelvic floor disorders in 56 women with ED. Diagnostic concordance between BD and MRID did not differ significantly. Concordance rates for MRID were 82% for rectocoele, 57% for perineal descent, 93% for enterocoele, and 55% for rectal intussusception. Pilkington et al. (2012) aimed to establish whether there were measurable differences between BD and MRID in 42 consecutive patients. Anismus

(functional dysfunction) was reported in 29% on BD and 43% on MRID. MRID missed 31% of rectal intussusceptions detected on BD. The agreement between grade of rectal intussusception was only fair (k=0.26), with MRID tending to underestimate this. Patients reported that they found it harder to empty their bowel lying in the MRI scanner. Indeed, complete rectal emptying occurred in only 2% of subjects on MRID compared with 29% on BD. This may have negatively impacted MRID sensitivity for detecting rectal intussusception. Zafar et al. (2017) reported similar findings in a prospective study of 55 patients with ED undergoing both techniques. BD detected more rectal intussusceptions than MRID. Again, though not statistically significant, patients achieved higher rates of rectal emptying during BD compared to MRID. Detection rates for rectocoele were similar, but BD revealed a significantly higher number of trapping rectocoeles compared to MRID. Furthermore, MRID appeared to underestimate the rectocoele size, although it was able to detect a significant number of anatomical abnormalities missed on BD in the anterior and middle pelvic floor compartments. Contrarily, however, higher MRID sensitivities for intussusception have been reported by the 2 most recent comparative studies (Martin-Martin et al. 2017, Poncelet et al. 2017). Nevertheless, pooled prevalence of the 5 comparative studies showed that BD was superior to MRID in the detection of intussusception (57.8% vs. 37.8%; OR, 1.52 [95%CI 1.12-2.14, p=0.009]), although the technique was associated with higher level of embarrassment (qualitatively measured among patients) and/or lower tolerance (54.3% vs. 30.0%; OR, 1.73 [95%CI 1.14-2.62, p=0.008]) (Figure 3.12).

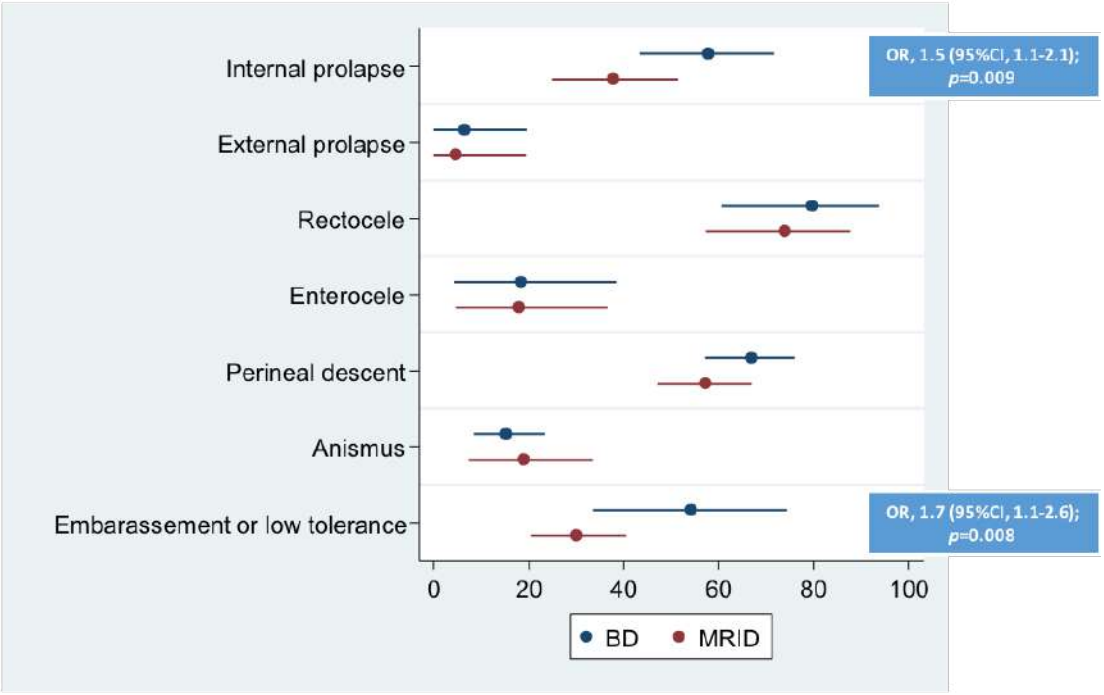


FIGURE 3.12 - POOLED PREVALENCE AND 95% CONFIDENCE INTERVAL (CI) FOR SPECIFIC FINDINGS ACCORDING TO RADIOLOGIC TECHNIQUE. KEY: BD = X-RAY BARIUM DEFAECOGRAPHY; MRID = MAGNETIC RESONANCE IMAGING DEFAECOGRAPHY; OR = ODDS RATIO.

3.7. Discussion

This systematic review and meta-analysis demonstrated that the prevalence of structural and functional abnormalities detected by defaecography was high, but varied considerably across studies, with high heterogeneity that may reflect variation in measurements, patients or procedural variations. Nevertheless, findings that may be considered truly pathological (i.e. not seen in health) were still frequently observed.

We must acknowledge that our pragmatic threshold of including studies reporting outcomes on more than 40 subjects (Figure 3.2) served to exclude small case series that often reported on early experience with the techniques, but also left out a significant number of studies from reputed and established institutions with high-quality research.

Structurally significant intussusception (i.e. recto-anal) and rectocoele (>4 cm depth) were found in one in four (23.7%) and one in six (15.9%) patients with symptoms of CC, respectively (Table 3.3). Interestingly, their prevalence was higher in prospective than retrospective studies (33.7 [21.0-47.6] vs. 17.1 [10.6-24.7], and 23.1 [14.5-32.9] vs. 11.6 [5.6-19.2], respectively). Despite being adopted by only 1 study (Adusumilli et al. 2013), the Oxford Prolapse Grade system can easily differentiate between an intra-rectal (grade I and II) and intra-anal (grade III and IV) intussuscepta and is the preferred method to assess prolapse severity in patients undergoing corrective surgical procedures (Grossi et al. 2017). Conversely, poor agreement was found between the 2 studies reporting on outcomes of BD in HV using the classification proposed by Shorvon et al. (1989): despite reporting on a similar gender ratio, the prevalence of intussusception in the study by Shorvon et al. (1989) was much higher than that reported by Palit et al. (2014) (70% vs 20%, respectively) and likely reflects the challenge in diagnosing minor clinically insignificant infolding (Stojkovic et al. 2000).

Despite a paucity of information in HV using BD (primarily for ethical reasons), these studies show that prevalence of structural abnormalities in health is not negligible and may lead to over-interpretation of BD, as has already been acknowledged (Bartolo et al. 1988). Interpreting intra-anal intussusception and large rectocoele as truly pathological is in keeping with the findings of Palit et al. (2014), who showed a rectocoele with mean depth of 2.5 ±0.7 cm in 26/28 (93%) and low grade (recto-rectal) intussusception in 20% of healthy female volunteers. Similarly, prevalence of >2 cm rectocoele, internal, and external prolapse were found in 62%, 11%, and 4%, respectively, in a recent study of 113 healthy females undergoing MRID (published later than final search date, hence not included in this systematic review) (Tirumanisetty et al. 2018).

Prevalence of enterocoele ranged from 0% on MRID (Goh et al. 2000) to 4% on BD (Shorvon et al. 1989). Given such low prevalence in health, enterocoele should be regarded as pathological, and this was found in about one in six CC (16.8%) patients.

The outcomes of this systematic review support the use of radiology alongside other common tests of ED (i.e. clinical examination, BET, and AM), to enable an accurate morphological assessment of the posterior pelvic floor compartment. The considerable disagreement between the results of all current modalities (Palit et al. 2016) highlights the need for a reappraisal of both diagnostic criteria and what represents the 'gold standard' investigation. One of the principle challenges will be to promote standardization of the technique so that results are transferrable between institutions.

Symptoms of constipation may also affect patients in the absence of any obstructive structural rectal or pelvic floor features. Spasm/hypertrophy of the puborectalis muscle was initially proposed as the main pathophysiologic mechanism in this CC subgroup by Wasserman (1964), who reported 4 cases of 'puborectalis syndrome', a condition subsequently named 'anismus' (Preston and Lennard-Jones 1985) or 'dyssynergia' (Meunier 1985, Merkel and Wald 1992). In its broadest sense, the latter term indicates a failure of recto-anal coordination during straining. Other synonyms included: 'spastic pelvic floor syndrome' (Kuijpers and Bleijenberg 1985), 'abdomen-levator incoordination' (Aubert et al. 1987), 'immobile perineum' (Pezim et al. 1987), and 'abdomino-pelvic asyncronism' (Emery et al. 1988). More recently, the term 'functional defaecation disorder' has been adopted by the Rome classification system to characterize paradoxical contraction or inadequate relaxation of the pelvic floor muscles and/or inadequate propulsive forces during attempted defaecation (Rao et al. 2016). In

this scenario, defaecography may have an important role in the study of recto-anal coordination, especially in light of recent evidence discrediting the diagnostic accuracy of anorectal manometry for dyssynergic defaecation (Grossi et al. 2016).

Finally, further studies should clarify whether patient position (supine in all included studies on MRID) may explain the increased sensitivity of BD over MRID in the detection of intussusception, being the former associated with higher rates of complete or nearly complete rectal emptying.

In conclusion, pathologically significant structural abnormalities, as well as functional abnormalities, are common in CC patients. Since structural abnormalities cannot be evaluated using non-imaging test modalities (balloon expulsion and anorectal manometry) (Table 3.7), defaecography should be considered first-line diagnostic test, if resources allow.

TABLE 3.7 - POOLED PREVALENCE FOR SPECIFIC FINDINGS ACCORDING TO TEST.

Test findings	Anorectal manometry[¶]	Balloon expulsion test[¶]	Defaecography
Normal	52%	60%	17%
Abnormal	48%[*]	40%[‡]	83%
Functional	100%	100%	24%
Structural	NA	NA	76%
Intussusception	NA	NA	29%[†]
Recto-anal (Oxford III-IV)	NA	NA	24%[†]
External prolapse (Oxford V)	NA	NA	5%[†]
Rectocoele >4 cm	NA	NA	16%[†]
Enterocoele	NA	NA	17%[†]
Megarectum	NA	NA	7%[†]
Dynamic perineal descent	NA	NA	45%[†]

[¶]*Data from a previous meta-analysis (Videlock et al. 2013). NA: not applicable.*

[†]*Truly pathological abnormalities (i.e. not seen in health).*

[*]*Defined as dyssynergic pattern (i.e. paradoxical contraction or inadequate relaxation of the anal sphincter on attempted defaecation).*

[‡]*Defined as patients unable to expel the balloon after 5 min seated on a commode.*

Chapter 4 - Systematic characterisation of defaecographic abnormalities in a consecutive series of 827 constipated patients and impact of sex.

4.1. Introduction

Symptoms of chronic constipation (CC) affect 14% of the general population in Western countries (Suares and Ford 2011), mostly resulting from a primary disturbance of bowel function due to dietary or lifestyle factors or from a disorder of colonic propulsion or rectal emptying (Camilleri et al. 2017). The latter (known as evacuation disorder [ED] (Cook et al. 2009)) results from inability to expel stools due to structural (e.g. intussusception, rectocoele, enterocoele) and/or functional causes (e.g. impaired recto-anal coordination) (Chapter 3).

Compared to non-radiological tests of evacuation and anorectal coordination (e.g. balloon expulsion test; anorectal manometry), defaecography is considered the reference standard for the assessment of pelvic floor anatomy and function, given its capability to dynamically evaluate rectal morphology (and other pelvic organs) during simulated defaecation (Grossi et al. 2018, Grossi et al. 2019).

However, a recurrent criticism of defaecography is the acknowledged overlap between health and disease (Rao et al. 2016), hampered by a paucity of normative data. Nevertheless, despite a significant heterogeneity of protocols and technical variations in published studies, a recent systematic review and meta-analysis derived specific

definitions and cut-offs to diagnose 'true abnormalities' (i.e. those rarely or never found in health) as shown in Chapter 3.

Although various abnormalities are acknowledged (Johansson et al. 1985, Mellgren et al. 1994, Gladman et al. 2003), the frequency with which they occur is poorly defined. Further, the breadth of overlap between various structural and functional abnormalities is unknown. The aim of this study was to systematically characterize defaecographic abnormalities in a consecutive series of patients presenting with moderate to severe symptoms of constipation. Secondary aims were to compare findings between genders.

4.2. Methods

4.2.1. Setting and Participants

All patients attending the GI Physiology Unit, at Barts Health NHS Trust for anorectal physiology testing had their data entered in a prospectively collected database. Through retrospective analysis, those presenting with a primary complaint of constipation (difficult and/or infrequent defaecation) with or without concomitant faecal incontinence, scoring ≥12 on the Cleveland Clinic Constipation score (CCCS) (Agachan et al. 1996), and undergoing defaecography between November 2012 and July 2015 were included within this cross-sectional study. Patients presenting with primary complaint of faecal incontinence and/or pelvic floor dysfunctions other than constipation, and those in whom defaecography was not technically possible (e.g. weight exceeding 150 Kg; uncontrolled anorectal pain; major incontinence on transfer to the commode precluding any interpretation of radiological imaging) were excluded.

4.2.2. Clinical assessment

All patients were screened for coexistent gastrointestinal disease and other relevant comorbidities using a comprehensive departmental questionnaire, which included validated scores for constipation (Agachan et al. 1996), faecal incontinence (Vaizey et al. 1999), irritable bowel syndrome (Drossman 2016), and joint hypermobility syndrome (Beighton et al. 1973), as well as structured surgical, medical and obstetric histories. Joint hypermobility was measured using the classification system proposed by Stewart and Burden (2004), which identifies three sub-categories of Beighton score: 0-3 (tight); 4-6 (hypermobile); and 7-9 (distinctly hypermobile). The 7-point Bristol Stool Form scale (Lewis and Heaton 1997) was used to categorized stools into 'hard' (score 1–2), 'normal' (score 3–4), 'loose' (score 5–7), or variable (i.e. more than one category selected).

4.2.3. GI physiology testing

In addition to defaecography, patients typically underwent a battery of lower GI physiology tests including high-resolution anorectal manometry, endoanal ultrasound, rectal sensation to balloon distension (hypersensitivity was defined as a maximum tolerated volume <75 mL, whereas hyposensitivity was diagnosed when ≥2 sensory thresholds were above normal limits (Townsend et al. 2016)), and whole gut transit study using radio-opaque markers. This latter test was limited to patients reporting infrequent (<3 per week) defaecation, and was performed by administration of a single set of markers (n=50). Delayed transit was defined as >20% retention of markers (Evans et al. 1992).

4.2.4. Defaecography

A detailed description of the technique has been published elsewhere (Palit et al. 2014). All measurements were taken as described below.

4.2.4.1. Static measurements

4.2.4.1.1. Rectal diameter

The mid-rectal diameter was determined by measuring a line drawn between the anterior and posterior walls of the rectum at its widest point (Gladman et al. 2007). If >8.1 cm in males or >6.9 cm in females, a diagnosis of megarectum was made (Palit et al. 2014) (Figure 4.1). The volume of neostool instilled to reach a strong sustained desire to defaecate was recorded.

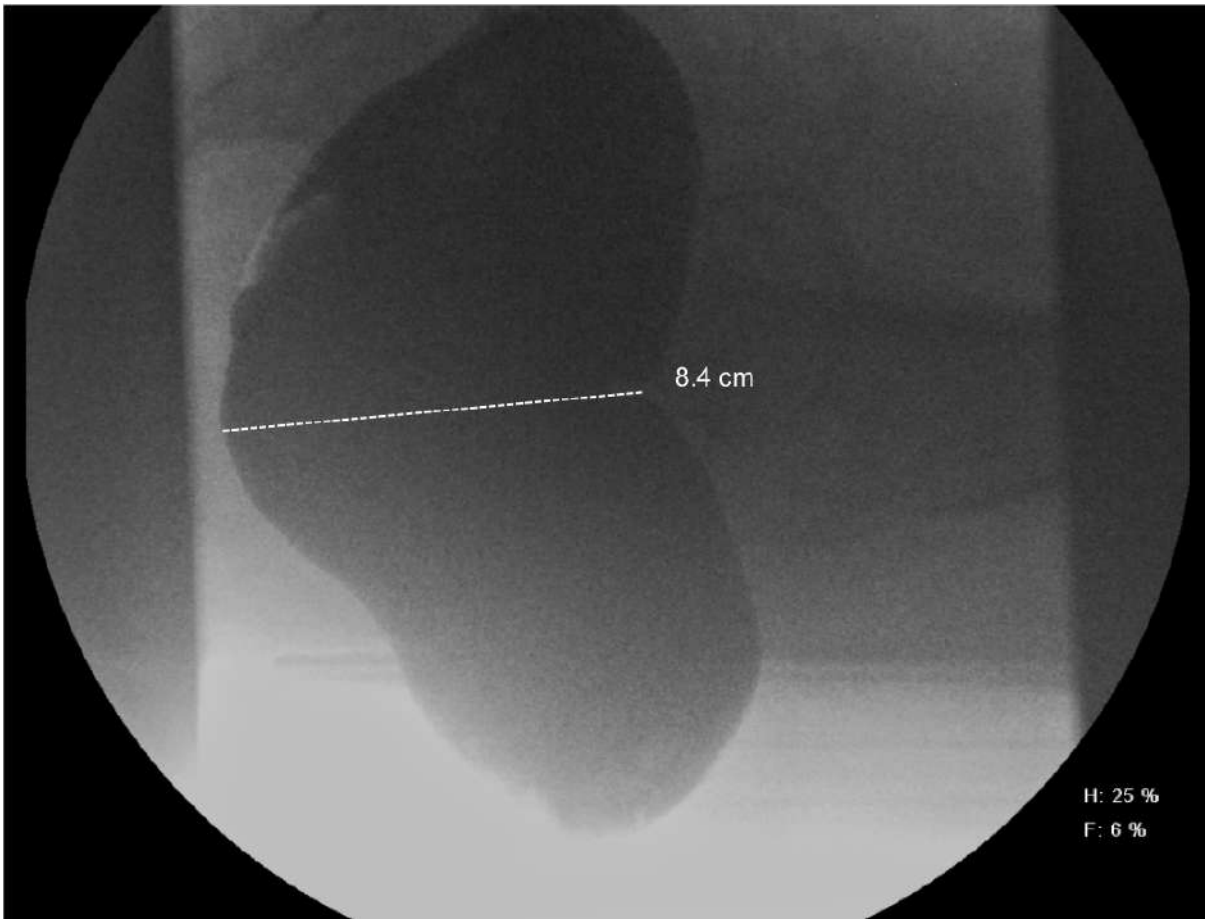


FIGURE 4.1 - MEGARECTUM DIAGNOSED IN A 79-YEAR-OLD FEMALE.

4.2.4.1.2. Posterior anorectal angle

The posterior anorectal angle (PARA) was defined as the angle between a tangential line drawn along the posterior edge of the rectal ampulla just proximal to the impression of the puborectalis and a line drawn along the axis of the anal canal. The angle was measured during rest, squeeze and maximum evacuatory effort. Based on the results of a previous study on healthy subjects (Palit et al. 2014), PARA at rest was categorized into one of the following: a) normal (males, 84-132°; females, 80-132°); b) hyper-obtuse (>132°); or c) hyper-acute (males, <84°; females, <80°) (Figure 4.2).

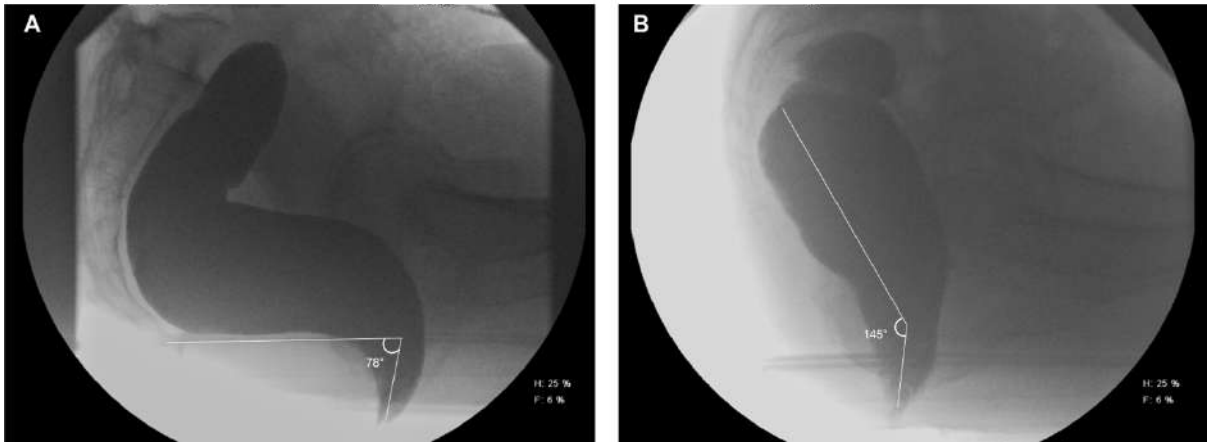


FIGURE 4.2 - POSTERIOR ANORECTAL ANGLE: HYPER-ACUTE IN A 45-YEAR-OLD FEMALE (A) AND HYPER-OBTUSE IN A 55-YEAR-OLD FEMALE (B).

4.2.4.1.3. Sigmoid progression of contrast

The amount of contrast migrating proximally into the sigmoid colon was calculated as a percentage of total contrast instilled prior to start evacuation (Figure 4.3).

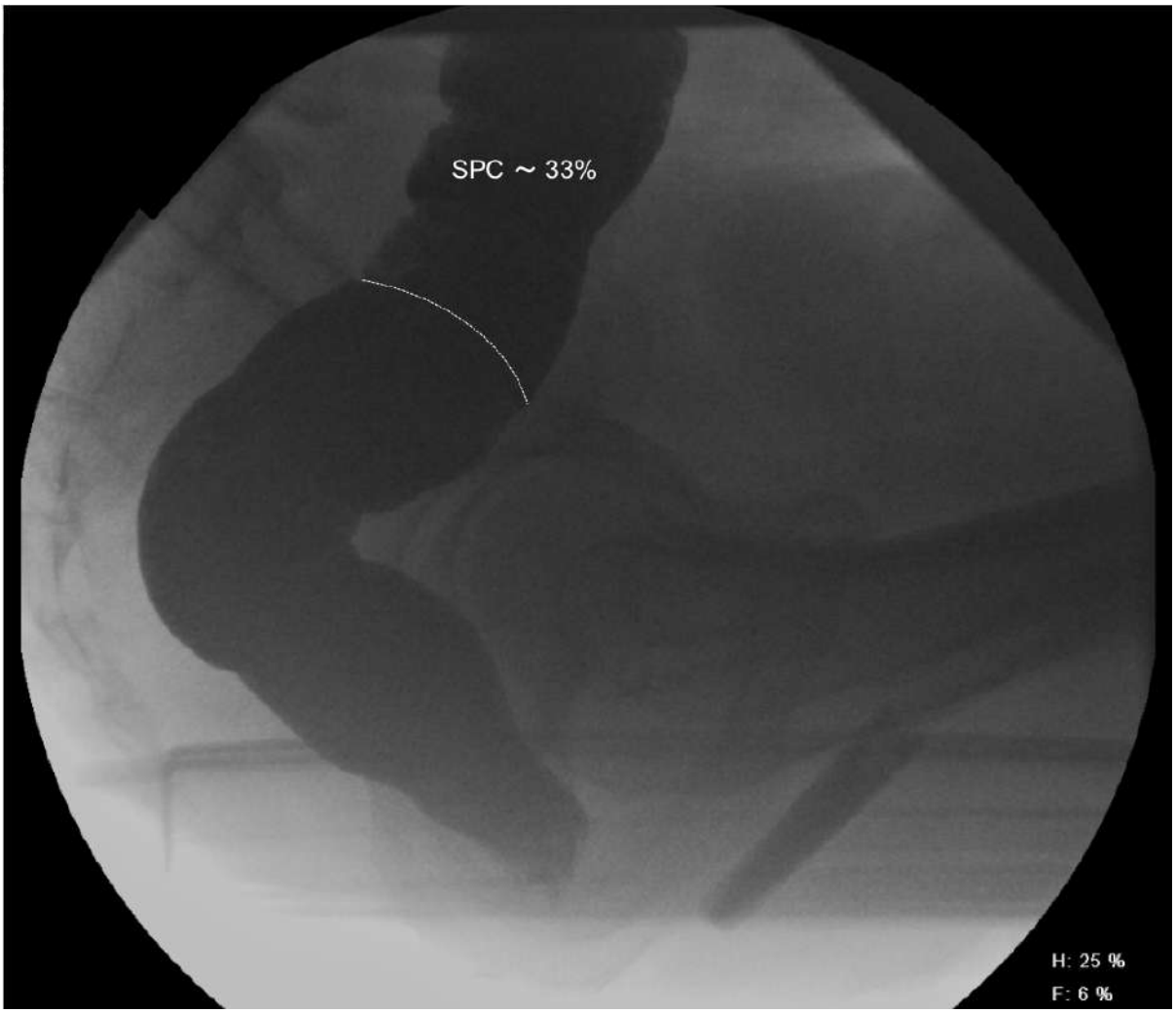


FIGURE 4.3- SIGMOID PROGRESSION OF CONTRAST (SPC) IN A 60-YEAR-OLD FEMALE. APPROXIMATELY ONE THIRD OF TOTAL CONTRAST INSTILLED PRIOR TO START EVACUATION MIGRATED INTO THE SIGMOID COLON. THE DOTTED LINE INDICATES THE RECTOSIGMOID JUNCTION.

4.2.4.2. Dynamic measurements

4.2.4.2.1. Structural abnormalities

4.2.4.2.1.1. Rectocoele

Defined as an outpouching of the rectal wall during maximal evacuatory effort (Mahieu et al. 1984). The height was measured as the length of a line running across the 'mouth' of the rectocoele, and the depth as the length of a line running perpendicularly from the line across the mouth to the apex of the bulge (Shorvon et al. 1989, Palit et al. 2014).

Based on the latter measurement, rectocoele size was determined (e.g. small [<2 cm]; medium [2-4 cm]; large [>4 cm]) (Mellgren et al. 1994). In addition, rectocoele morphology was defined according to Marti types I (digitiform), II (with a lax rectovaginal septum, an anterior mucosal prolapse and a deep pouch of Douglas), or III (associated with intussusception or even rectal prolapse) (Marti et al. 1999). The presence of contrast retained within the pouch was also recorded. Large rectocoeles (irrespective of symptoms) and medium rectocoeles (if present, together with at least one of the following complaints: a) sense of pelvic organ prolapse; b) digital assistance to aid faecal expulsion) were considered as structurally significant. Small rectocoeles were deemed as a variant of normality as were isolated medium trapping and asymptomatic rectocoeles (Table 4.1).

4.2.4.2.1.2. Rectal intussusception

Defined as an infolding of the rectal wall during straining and characterized using the Oxford Prolapse Grade system (Adusumilli et al. 2013). In addition, the presence of obstructive features were recorded. Any obstructing and Oxford grade 3-5 non-obstructing intussuscepta were considered as structurally significant, whereas non-obstructing Oxford 1-2 intussuscepta were not considered structurally relevant (Grossi et al. 2018), except for isolated diagnosis, in which case they were deemed as a normal variant (Table 4.1).

4.2.4.2.1.3. Enterocoele

Defined as a herniation of the posterior cul-de-sac downward between the vagina and rectum (Maglinte et al. 1997) and deemed as structurally significant in all cases.

4.2.4.2.1.4. Excessive dynamic perineal descent

Defined as descent of the anorectal junction during straining more than 3.5 cm from its resting position at the inferior plane of the ischial tuberosities (Karlbom et al. 1999).

TABLE 4.1 - DEFINITIONS OF STRUCTURAL ABNORMALITIES.

Structural abnormalities	**Significant**	**Insignificant**
Rectocoele*	>4 cm or 2-4 cm trapping and symptomatic	2-4 cm non trapping or 2-4 cm trapping and asymptomatic
Intussusception^	Oxford 3-5 or Obstructing Oxford 1-2	Non-obstructing Oxford 1-2
Enterocoele	Any	*NA*
Excessive dynamic perineal descent§	>3.5 cm	*NA*
Megarectum	Any	*NA*

NA: not applicable
**<2 cm or isolated 2-4 cm trapping and asymptomatic were considered normal variants*
^*Isolated non-obstructing Oxford 1-2 was considered normal variants*
§*≤3.5 cm was considered normal variant*

4.2.4.2.2. Functional abnormalities

One or more of the following criteria defined a functional abnormality on expulsive attempts (Palit et al. 2014, Heinrich et al. 2015, Palit et al. 2016): a) incomplete or absent opening of the PARA; b) incomplete or absent anal sphincter relaxation (maximal lower anal canal width <0.5 cm); c) ineffective propulsive forces (absent rectal mobility during push efforts).

4.2.4.2.3. Evacuatory efficiency

Each procedure was timed from the commencement of evacuatory effort to completion. The percentage of contrast expelled at end evacuation was calculated from the area of

contrast within the rectum at rest. Expulsion of at least 65% of neostool and/or evacuation within 150 seconds were considered as normal parameters (Palit et al. 2014).

4.2.5. Identification of defaecographic phenotypes

Eight binary variables (presence or absence) were used to identify a finite number of defaecographic phenotypes. These were:

- functional abnormality
- megarectum
- excessive dynamic perineal descent
- enterocoele
- intussusception
  - structurally significant intussusception
- rectocoele
  - structurally significant rectocoele

These variables in random combination could give rise to 128 (2^7) possible phenotypes. Venn diagrams and UpSet tool (Lex et al. 2014) were used for the quantitative analysis of sets, their intersections, and aggregates of intersections. UpSet is focused on creating task-driven aggregates, communicating the size and properties of aggregates and intersections, and a duality between the visualization of the elements in a dataset and their set membership. UpSet visualizes set intersections in a matrix layout and introduces aggregates based on groupings and queries. The matrix layout enables the effective representation of associated data, such as the number of elements in the aggregates and intersections. The elements represented in the sets and their associated

attributes are visualized in a separate view. UpSet is web-based and open source (https://vdl.sci.utah.edu/upset2/).

4.2.6. Operators and Assessors

Defaecography was performed by 9 different clinical practitioners throughout the study period, all appropriately trained and experienced in the procedure, and with the appropriate radiation protection certification. Measurements and morphologies were determined by the writer and Dr Henriette Heinrich upon inter-observer agreement calculations, with discrepancies resolved by Dr S Mark Scott.

4.2.7. Statistical analysis

Categorical variables across groups were compared by using Fisher's exact test or Pearson's chi-square test with Bonferroni correction for multiple comparisons; continuous variables were reported as mean (standard deviation, SD) or median (interquartile range, IQR) as appropriate. All analyses were performed using proprietary software (Stata V15.0; Stata Corp., College Station, Texas, USA). The Benjamini-Hochberg method was used to control the false discovery rate for gender comparisons (Benjamini and Hochberg 1995).

4.3. Results

4.3.1. Participants

A total of 832 subjects initially fulfilled criteria for inclusion. Of these, 5 patients (0.6%) were excluded due to major contrast loss on transfer to the commode precluding any reliable analysis. Of the remaining 827 patients (median age, 49 years; range, 17-98),

725 (87.7%) were female. Among these, 525 (72.4) were parous with a median of 2 (IQR, 2-4) childbirths. Two-hundred-eight (28.7%) patients had undergone hysterectomy.

4.3.2. Demographics and clinical characteristics

No statistically significant differences were found between genders for all comparisons except for CCCS, with marginally higher mean symptom severity (<1 full point of the scale) demonstrated in females compared to males (18.6 [3.6] vs. 17.5 [3.1], respectively; p=0.002) (Table 4.2).

TABLE 4.2 - PATIENTS' DEMOGRAPHICS AND CLINICAL CHARACTERISTICS.

Characteristics	**Total N=827**	**Females N=725**	**Males N=102**	***P***
Age, years	49.2 (15.2)	49.1 (15.0)	50.2 (16.5)	0.511
CCCS	18.5 (3.6)	18.6 (3.6)	17.5 (3.1)	**0.002**
St Marks Incontinence score	9.0 (6.4)	9.0 (6.4)	8.8 (6.6)	0.693
Beighton score*	1.8 (2.0)	1.8 (2.0)	1.6 (2.0)	0.532
Tight (0-3)	517 (84)	450 (84)	67 (86)	0.785
Hypermobile (4-6)	68 (11)	61 (11)	7 (9)	0.660
Distinctly hypermobile (7-9)	29 (5)	25 (5)	4 (5)	0.777
Bristol Stool Form scale				
Normal (3-4-5)	95 (11)	81 (11)	14 (14)	0.457
Hard (1-2)	211 (26)	187 (26)	24 (23)	0.534
Loose (6-7)	71 (9)	58 (8)	13 (13)	0.230
Variable	450 (54)	399 (55)	51 (50)	0.547
Irritable bowel syndrome (Rome IV criteria)**	278 (48)	248 (49)	30 (44)	0.463
Use of medications				
Opioids	151 (18)	129 (18)	22 (22)	0.431
Antidepressants	220 (27)	191 (26)	29 (28)	0.744
Rectal sensitivity***				
Normal	597 (79)	525 (78)	72 (81)	0.680
Hyposensitivity	120 (16)	105 (16)	15 (17)	0.894
Hypersensitivity	42 (5)	40 (6)	2 (2)	0.215
Colonic transit time****				
Normal	235 (59)	211 (59)	24 (65)	0.575
Delayed	162 (41)	149 (41)	13 (35)	

*Available for 614 (74%) of patients.

**Available for 575 (70%) of patients.

***Available for 759 (92%) of patients.

****Available for 397 (48%) of patients.

4.3.3. Defaecographic findings

4.3.3.1. Static measurements

No differences were found in terms of rectal diameter at rest and PARA between sexes. The mean volume of rectal contrast used was 248 (SD, 103) mL with no significant variation between sexes (p=0.87) (Table 4.3). The amount of sigmoid progression of contrast was higher in males (median [IQR], 10% [0-20]) compared to females (5 [0-15]) (p=0.031). Among those exhibiting >40% progression, 7% were males and 2% females (p=0.003).

4.3.3.2. Dynamic measurements

Volume of contrast expelled and prevalence of evacuatory inefficiency was similar between sexes (Table 4.3). However, expulsion time was shorter in males (90 [60-120]) compared to females (110 [60-120]) (p=0.049). Overall, defaecography was classified as normal in 136 (16.4%) patients. This group included 73 (8.8%) patients in whom no abnormalities were found and 63 (7.6%) patients with isolated structurally insignificant abnormalities. A total of 612 (74.0%) patients presented isolated structural abnormalities (61.4%) with 9.6% in combination with a functional abnormality (Figure 4.4).

Among structurally significant abnormalities (n=571), 50% (n=283) occurred in isolation and 50% (n=288) in combination (Figure 4.5). Isolated rectocoele and intussusception were the most prevalent phenotypes, accounting for 18% and 15%, respectively. When considering combined abnormalities, the association of intussusception and perineal descent was the most frequently encountered (10%).

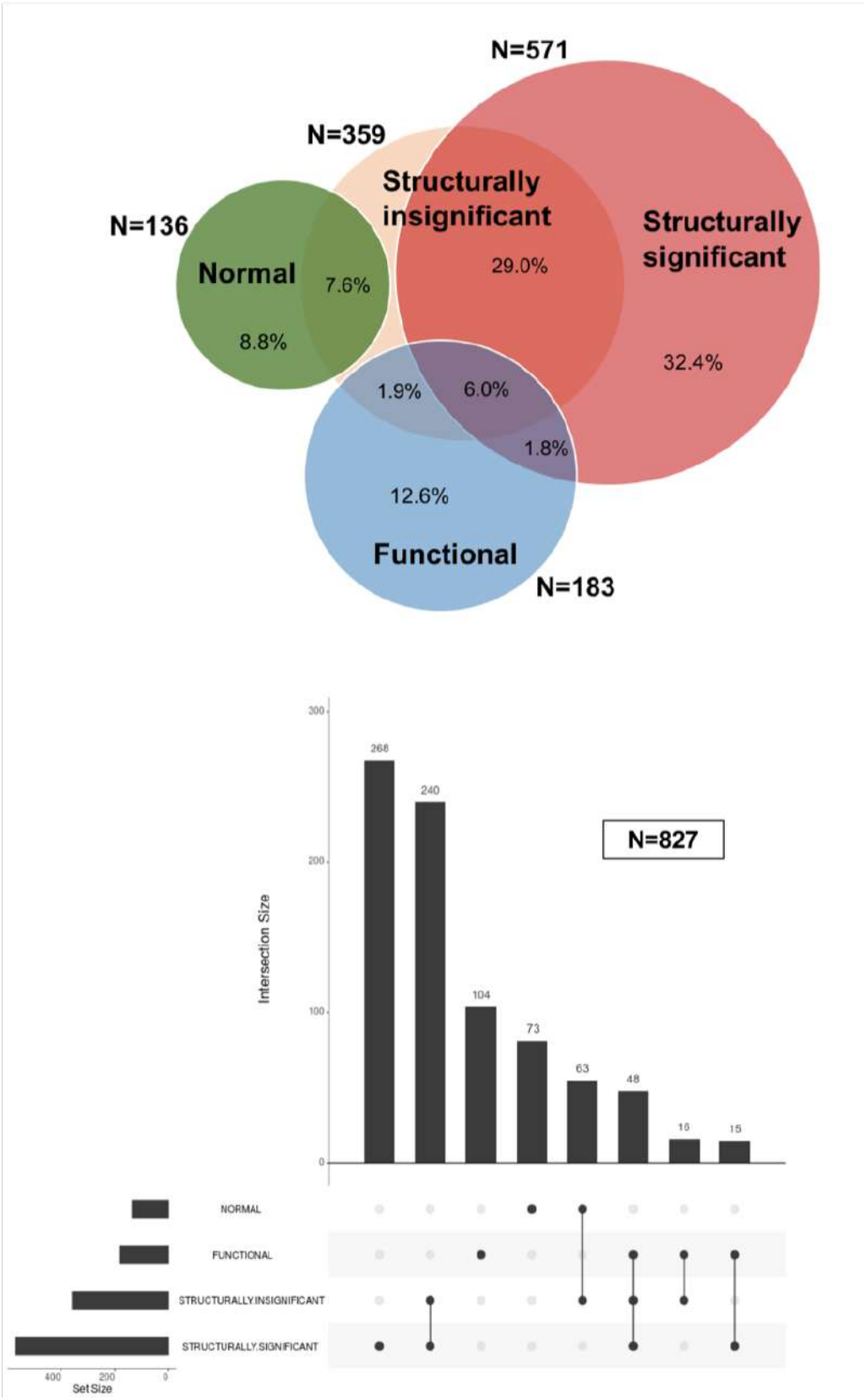


FIGURE 4.4 - OUTCOMES OF DEFAECOGRAPHY IN THE PATIENTS' COHORT. VENN'S DIAGRAMS (UP); UPSET GRAPH (DOWN).

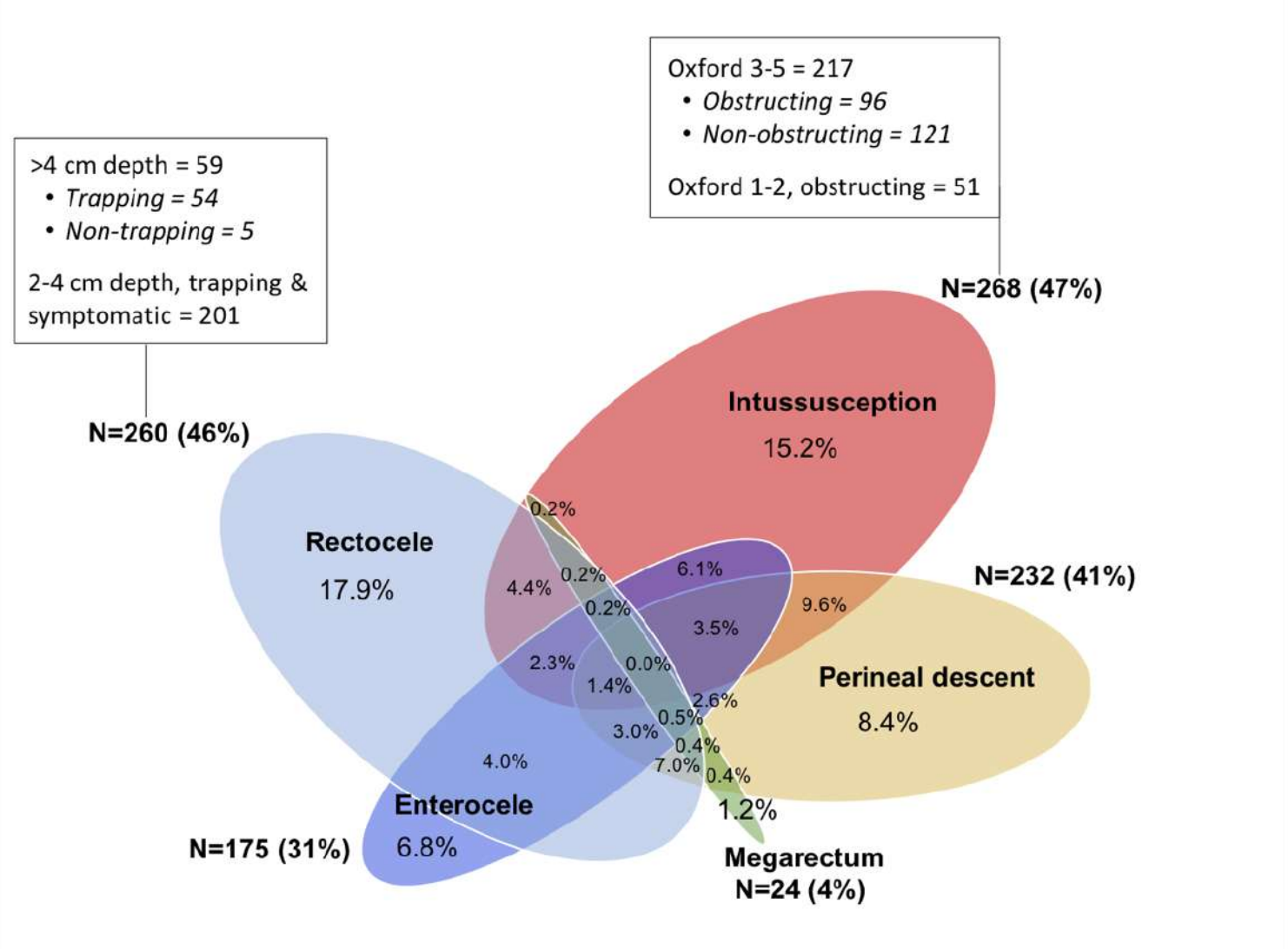


FIGURE 4.5 - (A) PREVALENCE OF STRUCTURAL ABNORMALITIES. VENN'S DIAGRAMS.

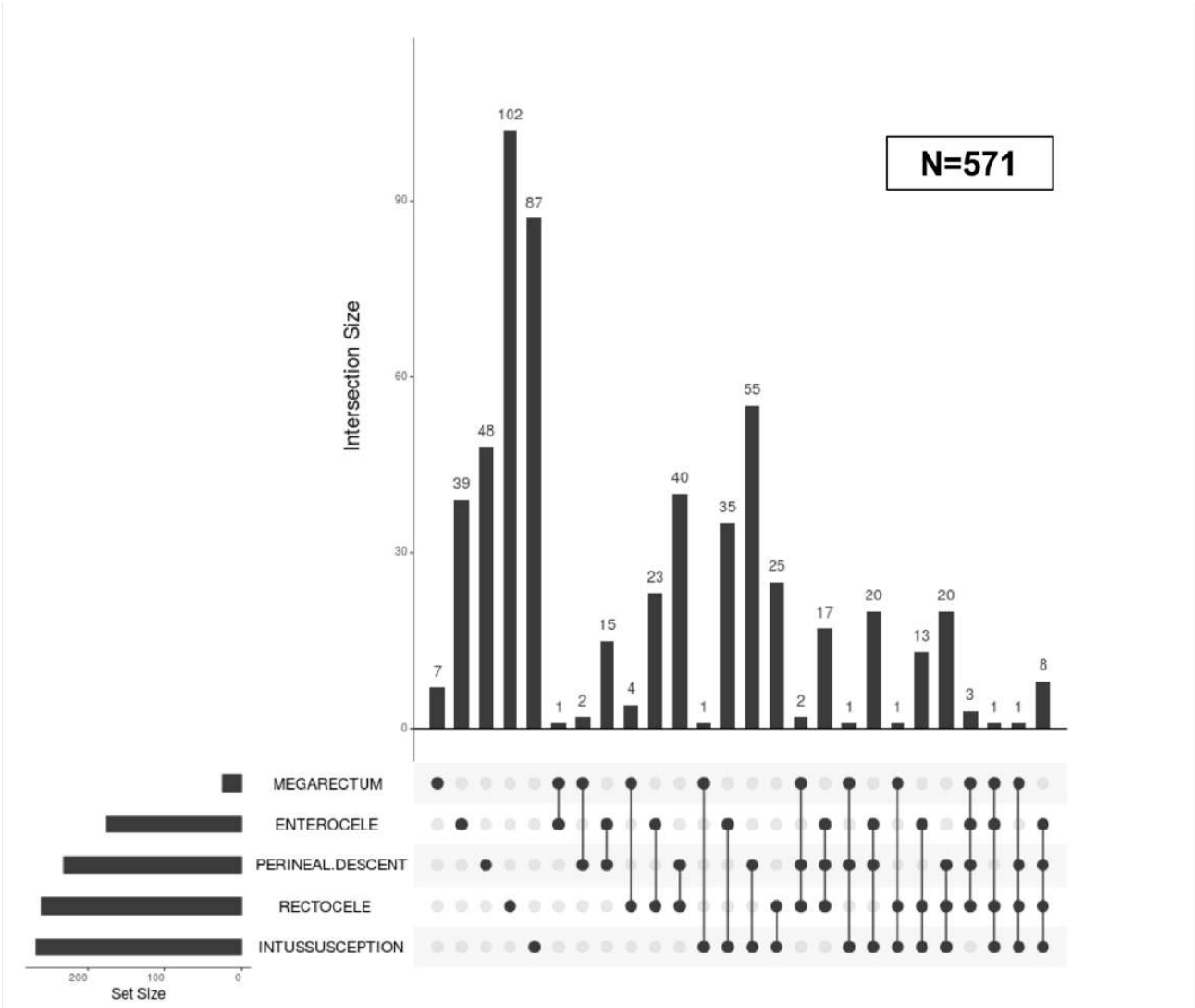


FIGURE 4.5 – (B) PREVALENCE OF STRUCTURAL ABNORMALITIES. UPSET GRAPH.

Functional abnormalities were detected in a larger proportion of males compared to females (29% vs. 21%, respectively; p=0.078) (Table 4.3). Structural abnormalities were much more prevalent in females (86% vs. 58% in males; p<0.0001), mainly due to the higher rate of significant rectocoeles in these patients (52% vs. 2% in males; p<0.0001). Rectocoele depth was greater in parous women compared to nulliparous (median, 2.7 [2.0-3.5] vs. 2.4 [2.0-2.9] cm, respectively; p=0.007). However, increasing parity was not associated with greater number of abnormalities. Although the rate of intussusception did not differ between genders, structurally insignificant intussuscepta were less frequently encountered in males compared to females (5% vs. 15%; p=0.016). Minor differences (not statistically significant) were noted in gender distribution of intussuscepta according to the Oxford Prolapse Grade system. Enterocoele and excessive dynamic perineal descent were also less frequently found in males compared to females (13% vs. 22%, p=0.036 and 15% vs. 30%, p=0.001, respectively).

TABLE 4.3 - DEFAECOGRAPHIC PARAMETERS AND FINDINGS.

	Total N=827	**Males N=102**	**Females N=725**	***P***
Volume of rectal contrast, %	248 (103)	246 (109)	248.2 (103)	0.868
Rectal diameter at rest	5.5 (4.2)	5.5 (1.5)	5.5 (4.4)	0.987
Sigmoid progression of contrast, %	5 (0-15)	10 (0-20)	5 (0-15)	0.031
<20	624 (76)	61 (63)	563 (78)	0.002†
20-40	177 (22)	29 (30)	148 (20)	0.048†
>40	18 (2)	7 (7)	11 (2)	**0.003†**
Posterior anorectal angle (PARA) at rest				
Normal	634 (77)	78 (75)	558 (77)	0.682
Hyper-acute	77 (9)	9 (9)	68 (9)	0.994
Hyper-obtuse	116 (14)	17 (16)	99 (14)	0.511
Volume of contrast expelled, ml	70 (60-80)	70 (55-80)	70 (60-80)	0.589
Expulsion time, sec	107 (60-120)	90 (60-120)	110 (60-120)	**0.049**
Normal defaecography	136 (16)	22 (22)	114 (16)	0.178
Evacuatory inefficiency	294 (36)	37 (36)	257 (35)	0.958
Functional abnormalities	183 (22)	30 (29)	153 (21)	0.078
Structural abnormalities	680 (82)	59 (58)	621 (86)	**<0.0001**
Significant	571 (69)	68 (67)	503 (69)	0.660
Insignificant	359 (43)	44 (43)	315 (43)	0.999
Normal variant	63 (8)	12 (12)	51 (7)	0.137
Intussusception	434 (53)	48 (47)	386 (53)	0.676
Significant	268 (32)	36 (35)	232 (32)	0.065
Obstructing Oxford 3-5	96 (12)	12 (12)	84 (12)	0.745
Non-obstructing Oxford 3-5	121 (15)	19 (19)	102 (14)	0.081
Obstructing Oxford 1-2	51 (6)	5 (5)	46 (6)	0.947
Insignificant	112 (14)	5 (5)	107 (15)	**0.016**
Normal variant	54 (7)	7 (7)	47 (6)	0.807
Oxford grade				
I	43 (10)	3 (6)	40 (11)	0.453

II	174 (40)	14 (29)	160 (42)	0.137
III	124 (28)	15 (31)	109 (28)	0.773
IV	77 (18)	13 (27)	64 (16)	0.106
V	16 (4)	3 (6)	13 (3)	0.402
Rectocoele	380 (46)	2 (2)	378 (52)	**<0.0001**
Significant	260 (31)	1 (1)	259 (36)	0.532
>4 cm trapping	54 (7)	0 (0)	54 (7)	0.999
>4 cm non trapping	5 (1)	0 (0)	5 (1)	0.999
2-4 cm trapping & symptomatic	201 (24)	1 (1)	200 (28)	0.099
Insignificant	88 (11)	1 (1)	87 (12)	0.410
Normal variant	32 (4)	0 (0)	32 (4)	0.999
Depth, cm	2.8 (1.0)	<2	2.8 (1.0)	**0.045**
Marti types				
I	112 (14)	0 (0)	112 (16)	0.999
II	188 (23)	1 (1)	187 (26)	0.999
III	80 (10)	1 (1)	79 (11)	0.377
Enterocoele	175 (21)	13 (13)	162 (22)	**0.036**
Megarectum	24 (3)	6 (6)	18 (3)	0.104
Excessive dynamic perineal descent	232 (28)	15 (15)	217 (30)	**0.001**

†*Bonferroni correction requires p≤0.017.*

4.3.4. Phenotypic variation and gender comparison

Out of 128 potentially identifiable phenotypes, a total of 72 (56%) were encountered (Figure 4.6).

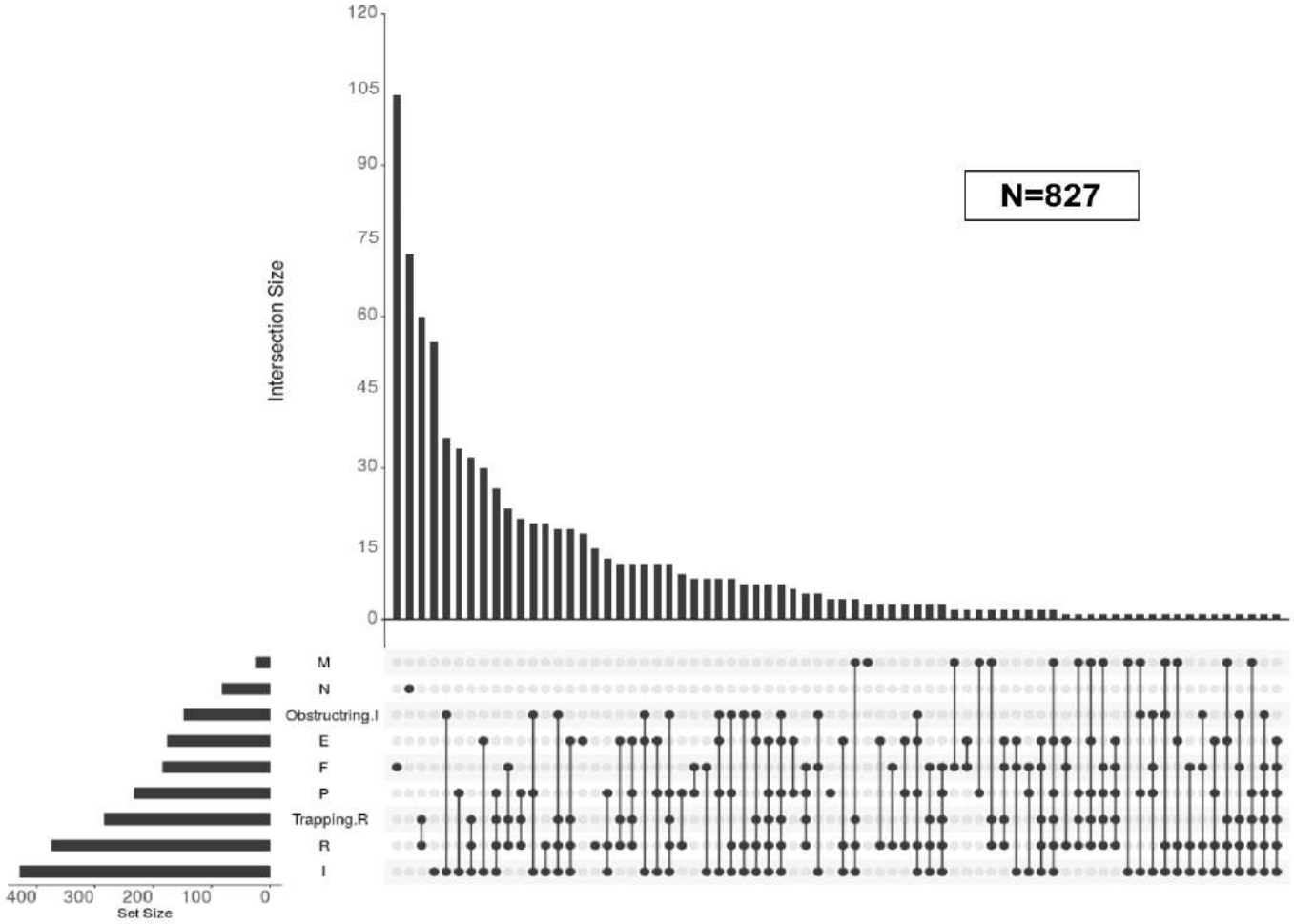


FIGURE 4.6 - PREVALENCE OF THE 72 PHENOTYPES ENCOUNTERED. UPSET GRAPH. M: MEGARECTUM; N: NORMAL; I: INTUSSUSCEPTION; E: ENTEROCOELE; F: FUNCTIONAL ABNORMALITIES; P: EXCESSIVE DYNAMIC PERINEAL DESCENT; R: RECTOCOELE.

The first 16 in descending order each included at least 2% of the total cohort and are listed in Table 4.4. These covered over two-thirds of total patients altogether (n=590, 71%). Patients with a normal defaecography (n=130 [16%]), including absence of any abnormalities (n=73 [9%] – phenotype II) and isolated insignificant intussusception (n=57 [7%] – phenotype IV), and those with an isolated functional abnormality (n=104 [13%] – phenotype I) were the most frequent (Table 4.4 and Figure 4.6). Adopting the Benjamini-Hochberg adjusted *P* value criterion at 0.003 (allowing to control the false discovery rate), a statistically significant difference among sexes was found for phenotypes I, II and IV (i.e. all were more prevalent in males than females).

TABLE 4.4 - DEFAECOGRAPHIC PARAMETERS AND FINDINGS.

Phenotypes		Total N=590 (71%)	Males N=86 (84%)	Females N=504 (70%)	*P* value
I	Functional abnormality	104 (13)	23 (23)	81 (11)	**.002**
II	Normal	73 (9)	20 (20)	53 (7)	**<.0001**
III	Sig. rectocoele	61 (7)	1 (1)	60 (8)	.004*
IV	Insig. intussusception	57 (7)	15 (15)	42 (6)	**.003**
V	Sig. intussusception	36 (4)	8 (8)	28 (4)	.072
VI	III + IV	36 (4)	0 (0)	36 (5)	.016*
VII	IV + EDPD	34 (4)	7 (7)	27 (4)	.175
VIII	IV + enterocoele	30 (4)	5 (5)	25 (3)	.403
IX	III + IV + EDPD	26 (3)	0 (0)	26 (4)	.063
X	I + III	22 (3)	0 (0)	22 (3)	.096
XI	III + EDPD	20 (2)	0 (0)	20 (3)	.158
XII	V + EDPD	19 (2)	4 (4)	15 (2)	.278
XIII	IV + Insig. rectocoele	19 (2)	1 (1)	18 (3)	.496
XIV	III + V	18 (2)	0 (0)	18 (3)	.151
XV	III + IV + enterocoele	18 (2)	0 (0)	18 (3)	.151
XVI	Enterocoele	17 (2)	2 (2)	15 (2)	.999

EDPD: excessive dynamic perineal descent.
**Bonferroni method requires p<.003.*

4.4. Discussion

4.4.1. Summary of main results

This is the first study to systematically review defaecographic phenotypes in constipation using rigorous methodology, with data compared to those derived from healthy subjects (Palit et al. 2014) and recently summarised in a systematic review and meta-analysis (Grossi et al. 2018). Moreover, this study provides phenotypic characterization of the largest series ever reported of male patients with moderate to severe symptoms of constipation.

Our analysis has shown that multiple structural and functional abnormalities may coexist in the same subject, with degree of overlap greater than previously recognized. The principal phenotypes encountered were normal defaecography (16%) and isolated functional abnormalities (13%), both significantly more prevalent in males than females. Coexistence of structural abnormalities was significantly more often encountered in females, reflecting global pelvic floor weakness. The number of phenotypes including at least 2% of patients were more limited in males (n= 10) compared to females (n= 16).

4.4.2. Comparison with previous studies

The first systematic description of defaecographic normality was published by Mahieu et al. (1984) who studied 56 asymptomatic subjects. Normal recto-anal dynamics were based on characterisation of 5 radiological features: (a) increase in the anorectal angle; (b) obliteration of the impression of the puborectalis muscle; (c) wide opening of the anal canal; (d) total evacuation of the rectal contents; (e) normal resistance of the pelvic floor.

Ahlback and Broden (1978) reported the first large series of defaecographies in 781 patients with clinically suspected intussusception. Since that time, 7 large case series (>250 patients) have been published (Table 4.5). Only 3 of these exclusively focused on patients with constipation (Sunderland et al. 1992, Dvorkin et al. 2005, Bozkurt et al. 2014). The others included a mixture of anorectal dysfunctions without providing stratified results on constipated patients. Emblematic is the paper by Mellgren et al. (1994) on 2,816 patients (superseding Ahlback and Broden (1978)), two thirds of whom were constipated (Table 4.5). Despite being the largest series ever reported, this study is limited by its duration (32 years) and the high number (n=7) of assessors involved in the interpretation of defaecographic data, with methodological changes that may have influenced the outcomes throughout the study length. The low prevalence of functional abnormalities (4%) is certainly underestimated as it was not recorded during the first 20 years of experience.

The majority of series in Table 4.5 aimed to determine the prevalence of structural and functional abnormalities as separate entities. The study by Grassi et al. (1994) is the only one that provides details about the coexistence of both abnormalities. Despite reporting on various anorectal dysfunctions, with at least two third being constipation, 8% of patients were diagnosed with combined structural and functional abnormalities, which is similar to the prevalence observed in our series (10%).

Among structural abnormalities, our prevalence of significant intussusception (28%) is equivalent to that reported by Mahieu et al. (1984) (23%) and Dvorkin et al. (2005) (25%). Prevalence of rectocoele in other studies varies from 22% to 89%, mainly secondary to heterogeneity in definitions and cut-offs adopted to diagnose significant

rectocoeles. The latter point is of crucial importance given the high prevalence of rectocoele in healthy women (Palit et al. 2014). If considering small or isolated trapping/asymptomatic medium-sized rectocoeles as a variant of normality (Table 4.1), prevalence of rectocoeles did not reach 50% in our series, with slightly less than one third (31%) being significant.

Prevalence of enterocoele (21%) was slightly higher than that reported by Mellgren et al. (1994) (19%) and Agachan et al. (1996) (16%), likely due to the inclusion of patients with anorectal dysfunctions other than constipation (e.g. faecal incontinence) in these two studies.

Prevalence of excessive dynamic perineal descent was double in women compared to men (30% vs. 15%), with a greater ratio than that reported by Andrade et al. (2014) using the same cut-off for diagnosis (22% vs. 17%).

Prevalence of functional abnormalities in previously published studies ranges between 8% and 29%, likely as a consequence of methodological variations among studies (e.g. using fixed or defaecatory desire contrast volumes and heterogeneity in definitions). The overall prevalence observed in our series was slightly lower than that reported by Agachan et al. (1996), possibly due to the higher number of males included in their compared to our study (24% vs. 12%, respectively).

There is also large variation in the prevalence of normality among studies, ranging from 8% to 38%. The 16% rate observed in our series resulted from the adoption of rigorous methodology derived from previous studies on healthy subjects (Palit et al. 2014, Grossi et al. 2018), and was 3 times more likely to occur in males compared to females.

TABLE 4.5 - DEFAECOGRAPHIC FINDINGS IN STUDIES REPORTING ON >250 PATIENTS AFTER MAHIEU ET AL. (1984).

First author	Year	No. (F, %)	Mean age	Inclusion criteria	CC %	Vol. (ml)	Duration (years)	Assessors (No.)	Normal %	Abnormalities						
										Structural % (significant I and R, %)					Functional %	Combined %
										I	EP	R	E	EDPD		
Mahieu	1984	132 (77)	46	CC	100	300	NR	NR	28	31 (23)	5	22 (22)	NR	1	NR	NR
Sunderland	1992	288 (82)	47	CC	100	120	NR	NR	38	6 (NR)	1	23 (NR)	NR	21	26	NR
Mellgren^	1994	2816 (84)	54	Mixed disorders	67	NR	32.0	7	23	31 (NR)	13	27 (NR)	19	9	4*	NR
Grassi	1994	564 (72)	53	Mixed disorders	~70	150	3.0	NR	NR	15 (NR)	2	60 (NR)	NR	10	15	8
Agachan	1996	744 (76)	64	Mixed disorders	60	DDV	7.0	NR	12	30 (NR)	8	41 (10)	16	35	29	NR
Dvorkin	2005	896 (81)	48	Mixed disorders	100	DDV	7.5	2	12°	31 (25)	NR	89 (NR)	NR	NR	12°	NR
Andrade	2014	290 (92)	58	Mixed disorders	NR	DDV	2.7	2	8	33 (NR)	4	60 (NR)	NR	22	12	NR
Bozkurt	2014	630 (93)	46	Rome III CC	100	NR	3.5	NR	9	42 (NR)	NR	79 (NR)	NR	3	8	NR
Grossi	2019	827 (88)	49	CC with CCCS ≥12	100	DDV	2.8	2	16	49 (28)	4	46 (31)	21	28	22	10

F: females; CC: chronic constipation; CCCS: Cleveland Clinic Constipation score; I: intussusception; EP: external prolapse; R: rectocoele; E: enterocoele; EDPD: excessive dynamic perineal descent; NR: not recorded; DDV: defaecatory desire volume.

^Superseded Ahlback and Broden (1978)

**Underestimated as only recorded since 1980*

°Combined normal or functional abnormalities

4.4.3. Implications for research and clinical practice

Coexistence of structural and functional abnormalities has certain important implications for management. Detection of a "functional" obstruction may be amenable to other management approaches such as biofeedback. Nevertheless, defaecography is widely used to direct the surgical approach in patients with constipation / evacuatory dysfunction allied to pelvic organ prolapse (e.g. rectocoele, high-grade intussusception), where the operation is dependent on reversal of the demonstrated anatomical abnormality. As extensively demonstrated, surgical outcomes are often suboptimal given the frequent overlap between various organic, functional and psychological factors in the same patient (Pescatori et al. 2007). However, since there are no randomised trials or prospective stratified studies in this field, it is impossible to judge whether the distinction of a radiologically significant finding from one seen in health affects outcomes, at least based on the published literature. The surgical community increasingly depends on the distinction between a "physiological" and "pathological" entity, since litigation and intense media scrutiny force surgeons to rigidly objectify their motivation for offering surgery (especially mesh and stapling) (https://www.classaction.org/transvaginal-mesh-lawsuit. Accessed June 26, 2019.). Accordingly, a UK position statement has been written (Mercer-Jones et al. 2017).

In conclusion, truly pathological significant structural abnormalities (i.e. those not seen in health) and functional abnormalities are common in patients with chronic constipation. The primary goal for any useful clinical test is to provide the correct diagnosis. Nevertheless, high quality, pragmatic randomised trials, addressing test standardisation and the impact of results on outcomes, are necessary.

Chapter 5 - Hitching procedures for the rectum (rectal suspension): graded practice recommendations from a systematic review and meta-analysis

5.1 Background and procedural variations

Constipation is common in adults and children with up to 20% of the population reporting symptoms depending on the definition used (2-28% adults; 0.7-30% children) (Stewart et al. 1999, van den Berg et al. 2006, Suares and Ford 2011). Chronic constipation (CC), usually defined as more than 6 months of symptoms, is less common but results in 0.5 million UK GP consultations per annum. A proportion of the population suffer symptoms that are both chronic and more disabling (probably about 0.4% population) (Shafe et al. 2011). Such patients, who are predominantly female (Knowles et al. 2003), are usually referred to secondary care with many progressing to tertiary specialist investigation. Patient dissatisfaction is high in this group; nearly 80% feel that laxative therapy is unsatisfactory (Wald et al. 2008) and the effect of symptoms on measured quality of life (QOL) is significant (Irvine et al. 2002).

The management of CC is a major problem due to its high prevalence and lack of widespread specialist expertise. In general, a step-wise approach is undertaken, with first line conservative treatment such as lifestyle advice and laxatives (primary care) followed by nurse-led bowel re-training programs, sometimes including focused biofeedback and psychosocial support (secondary/tertiary care). Although these treatments may improve symptoms in more than half of patients (Woodward et al.

2014), patients with intractable symptoms and impaired QOL may subsequently be offered a range of surgical interventions.

Surgical decision-making is greatly influenced by local expertise, commissioning or reimbursement, and personal enthusiasm for particular interventions. While robust diagnosis of specific pathophysiologies combined with multidisciplinary team discussion may help direct surgery, in the absence of an agreed pathway (e.g. published algorithm) to stratify patients, there is a current large and difficult-to-justify variation in surgical practice that continues to risk inadequately-informed and potentially harmful interventions being offered to poor surgical candidates. The need to reduce such variations in practice, based on available evidence, has been a recurrent theme of recent national specialty group discussions (e.g. Association of Coloproctology of Great Britain and Ireland [ACPGBI]) with various initiatives proposed. As part of the Chronic Constipation Treatment PathwaY (CapaCiTY) programme funded by National Institute of Health Research (NIHR), a multi-disciplinary working group was convened in July 2014 to address this need. This group of medical and nursing experts included members of The Pelvic Floor Society and urogynaecology expertise derived from the International Continence Society (ICS). As a prelude to developing new evidence from trials within the CapaCiTY programme, it was agreed that the current surgical evidence base would benefit from coalescence in the form of systematic review and graded practice recommendations. A decision was taken by the review team that results would be grouped by five main approaches to surgically treating chronic constipation: (1) colonic resection, (2) hitching procedures of the rectum (rectal suspension); (3) excisional procedures of the rectal wall (rectal excision); (4) reinforcement of the rectovaginal

septum (RV reinforcement); and (5) sacral nerve stimulation (SNS). This chapter reports the outcomes of rectal suspension procedures in adults presenting with CC symptoms.

5.2 Methods

5.2.1. Protocol and registration

The authors developed the protocol for review, detailing pre-specified methods of the analysis and eligibility for the review in accord with 2009 PRISMA guidance (Liberati et al. 2009) using also the new reporting elements derived from the 2016 harms checklist (Zorzela et al. 2016). While the protocol was not registered, a description of the NIHR CapaCITY programme is available in the public domain (http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=17784) and was presented nationally (DDF meeting, London 2015; National Pelvic Floor Meeting, Manchester 2015).

5.2.2. Eligibility criteria

5.2.2.1. Study characteristics

Study characteristics were defined using the PICOS framework. Search term definitions were inclusive, promoting a sensitive search of studies reporting surgical interventions for chronic constipation.

Population: The review aimed to identify studies of patients undergoing surgical interventions with the primary intent of treating chronic constipation. The definition of chronic constipation is neither straightforward nor uniformly applied (Cook et al. 2009). On this basis, all common terms encompassing problematic defaecation were used (Table 5.1).

TABLE 5.1 – SEARCH STRATEGY

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Population terms

"constipation"[All Fields] OR "obstructed defaecation"[All Fields] OR "colonic inertia"[All Fields] OR "intussusception"[All Fields] OR "rectal prolapse"[All Fields] OR “outlet obstruction”[All fields] OR "SRUS"[All Fields] OR "solitary rectal"[All Fields] OR "defaecation disorder"[All Fields]) OR “impaired defaecation”[All Fields] OR “rectal emptying”[All Fields] OR “bowel dysfunction”[All Fields] OR “bowel function”[All Fields] OR “defaecography”[All Fields] OR “defaecography”[All Fields] OR “defaecographic”[All Fields] OR “evacuation difficulty”[All Fields] OR “evacuation disorder”[All Fields] OR ("Constipation"[Mesh Terms]) NOT ("child"[MeSH Terms]).

-

Intervention terms

“Delorme procedure”[All Fields] OR "delormes procedure"[All Fields] OR "delorme's procedure"[All Fields] OR “sacral nerve stimulation”[All Fields] OR “sacral neuromodulation”[All Fields] OR “neurostimulation”[All Fields] OR “sacral nerve modulation”[All Fields] OR "STARR”[All Fields] OR "stapled transanal resection"[All Fields] OR “stapled transanal rectal resection” [All Fields] OR "trans-STARR"[All Fields] OR “Stapled trans-anal rectal resection”[All Fields] OR "rectopexy"[All Fields] OR "sacrocolpopexy"[All Fields] OR "sacropexy"[All Fields] OR "promontofixation"[All Fields] OR “colectomy”[All Fields] OR “proctocolectomy”[All Fields] OR “ileorectal”[All Fields] OR “cecorectal” [All Fields] OR “ileoproctostomy”[All Fields] OR “cecoproctostomy”[All Fields] OR “ileosigmoid”[All Fields] OR "rectocoele repair"[All Fields] OR "posterior repair"[All Fields] OR “colporrhaphy”[All Fields] OR “rectovaginal septum reinforcement”[All Fields] OR “anterior rectal wall repair”[All Fields] OR “surgical repair of rectocoele”[All Fields] OR ("transperineal mesh repair”[All Fields] OR “transperineal repair”[All Fields] OR “transvaginal repair”[All Fields] OR “transanal repair”[All Fields] OR “endorectal repair”[All Fields] OR “transrectal repair”[All Fields] OR “transanal longitudinal plication”[All Fields] OR ("Constipation/surgery"[Mesh Terms])

-

Report terms

(hasabstract[text]) AND ("0001/01/01"[PDat] : "2016/02/22"[PDat])

-

However, several pelvic floor procedures may be performed commonly for non-chronic constipation indications. Examples include pelvic organ prolapse syndromes where the physical prolapse or other organ dysfunctions of the vagina or bladder are the main motivation for surgery. While such patients invariably also have some degree of defaecatory problems, and their perioperative data could still be used to inform procedural safety, these patients may phenotypically differ at baseline and in response to surgical intervention even if the intervention itself is identical or at least similar. Cochrane reviews such as 'surgical repair of pelvic organ prolapse in women' (Maher et al. 2010) and of surgical management of external rectal prolapse (Tou et al. 2015) include some RCTs where defaecatory symptoms are recorded as a secondary outcome or as a complication but not as a primary presenting complaint of the population studied. These were considered ineligible for inclusion. Some studies reported outcomes on two populations, only one of which was eligible e.g. internal and external rectal prolapse. Where such data could not be separated by population, the study was also deemed ineligible for inclusion.

A minimum population sample of 20 patients was imposed for eligibility. This threshold was taken to exclude case reports and small case series that often reported a single surgeon's personal experience or early experience of experimental procedures.

Intervention: Surgical procedures for chronic constipation are subject to heterogeneous descriptions. On this basis, an iterative approach was taken by cross referencing e.g. with textbook reference lists to ensure that all terms in common usage were incorporated in the eventual search strategy. These included some genuine procedural variations but also multiple small changes in syntax for the same procedure.

Comparisons: Studies were eligible regardless of whether they were retrospective or prospective in design, controlled or uncontrolled. Only a minority of studies reported more than one procedure or more than one population.

Outcomes: Studies were broadly eligible if they provided extractable data on benefit (treatment efficacy), risk (harms) or both. For efficacy, inclusion necessitated the acceptance of the huge disparity in quality of outcomes reporting that are well acknowledged in the literature (Woodward et al. 2014), with a heavy reliance on estimates of global patient satisfaction with the procedure (an indirect measure of the patients own judgement of their post-operative state compared to their pre-operative state). Studies of physiological and anatomical outcomes alone were excluded since these are generally regarded as a poor surrogate of efficacy in this patient population (Knowles et al. 2009). Because the outcomes of surgical interventions for chronic constipation are known to exhibit a 'honeymoon period' in the months immediately following surgery, a minimum (mean or median) follow up of 12 months was applied for eligibility. It is acknowledged that enforcement of this criteria excluded some level I studies. Several studies reported the outcomes of more than one procedure. Where such data could not be separated by procedure, these were not included (often resulting in study ineligibility).

5.2.2.2. Report characteristics

Year of publication: Any publication date was eligible as covered by database search from 1960 to the date of final search (22nd February 2016).

Language: Due to the large number of studies retrieved, it was decided to include only studies with full text in the English language. While the numbers of foreign language

studies were small, these have been detailed for the reader in 'reasons for exclusion' at the full-text stage (rather than at the abstract screening stage).

Type of study: Only peer-reviewed publications reporting primary data were eligible. Thus reviews, editorials, letters and other forms of secondary expert opinion were excluded at the screening stage. Only full manuscripts were eligible thus conference abstracts and proceedings were also excluded. No constraint was imposed based on level of evidence. This decision was taken in the knowledge that the vast majority of data would be extracted from case series rather than higher quality study types.

5.2.3. Information sources

We performed a comprehensive search of the literature on 22nd February 2016 using PubMed and Evidence Based Medicine reviews (including the Cochrane database of systematic reviews and the Cochrane central register of controlled trials). A preliminary search in 2014 had determined that Embase and Web of Science led to almost 2000 duplicate records with no additional yield. Search terms used a sensitive combination of population, intervention and report terms. A keyword and hand search were used within relevant Cochrane systematic reviews. The specific search terms are listed in Table 5.1.

5.2.4. Study selection

Screening was performed at the abstract level, excluding studies not meeting eligibility criteria where this could be readily determined from the abstract alone. Full-text copies of all remaining English language studies were obtained and assessed by reviewers, who were un-blinded to the names of studies, authors, institutions or publications.

Disagreement regarding inclusion was resolved a senior author. Duplicate data sets generated from the same cohort of patients were excluded with the larger population size and longer follow-up cohort included at the expense of earlier reports from the same cohort. In instances of doubt, authors from the relevant institutions were contacted to confirm or refute any repetition of results (performed on 3 occasions).

Search results were cross-referenced to bibliographies from other sources (previous reviews and book chapters). Care was taken that any studies missed by the original search met the strict inclusion criteria and did not circumnavigate the carefully defined search strategy especially in relation to population terms.

5.2.5. Data collection process

Outcome data were extracted to a standardized template (Microsoft Excel spreadsheet) including study characteristics and outcome data (see below). One reviewer extracted the data and one verified content.

5.2.6. Data items

A full list of data fields is included in Table 5.2 (with annotation). These followed the PICOS framework with outcomes broadly divided into those assessing harms (intra- and perioperative complications and long-term adverse outcomes), and those assessing efficacy: global success ratings and functional outcomes (organized into validated symptom, QOL scoring instruments and individual symptoms). For perioperative complications, some consideration was given to classifying complications by established systems (e.g. Clavien-Dindo). However, inconsistencies in reporting made this unfeasible. Data were not collected in relation to cost effectiveness which was deemed

to fall outside the remit of the process aims. To simplify data extraction and presentation, for ordinal data, summary statistics were extracted as mean or median (with standard deviation when provided).

TABLE 5.2 - DATA FIELD FOR SYSTEMATIC REVIEW

Data extract	Description	Notes
Study characteristics		
First author	Text (num)	With citation number
Year publication	Text	To 2016
Number of patients	Number	Ordinal integer
Follow up	Months	Mean or median as documented in study (integer)
Study design	Text abbreviation	As Oxford CEBM levels of evidence
Evidence grade *	IA - IV	As Oxford CEBM levels of evidence
Population		
Disease	Text abbreviation	As supplied key
Sex ratio	Female: male	Ratio not simplified
Age	Years (integer)	Mean or median as supplied (range)
Intervention		
Operation (s)	Text abbreviation	As supplied key
Op duration	Minutes	Mean (integer)
Length of stay	Days	Mean to 1 decimal place
Outcomes		
Harms:		
Perioperative		
Total cx	Percentage	% to 1 decimal place
Infective cx	Percentage	% to 1 decimal place
Bleeding cx	Percentage	% to 1 decimal place
Proc specific cx	Percentage	As per specific procedure: % to 1 decimal place
Mortality	Percentage	% to 1 decimal place
Repeat intervention	Percentage	Generally, procedure specific for complications or poor functional outcome
Mortality rate	Number	Absolute number over reported denominator
Adverse long-term symptoms	Percentage	Some procedural specificity: Includes re-operation rate where relevant
Efficacy:		
Global success rating	Scale	Very commonly employed: % patients with good or excellent outcomes unless specified
Symptom scores	Count	Several variably validated summative scoring instruments: Pre and post or post only as available: mean + SD
Individual symptoms	Percentage	Some procedural specificity: Pre and post or post only as available
QOL measures	Count or scale	Few instruments used: Pre and post or post only as available: mean + SD

Cx: complications; SD: standard deviation.

5.2.7. Individual study quality and risk of bias

The methodological quality of all individual included studies was assessed and classified in accord with Oxford CEBM levels of evidence definitions for 'therapy or harm' (Zorzela et al. 2016). The following rules were applied accepting that distinguishing study designs can be problematic for observational studies (Dekkers et al. 2012):

(a) A study was deemed prospective if this was categorically stated or if patients were 'enrolled' or 'recruited' to a study that systematically recorded pre- and post-operative data. All other studies were assumed to be retrospective.

(b) A cohort study was defined as one designed to address a clear stated aim or hypothesis using specified analytical methods. In general, these included a comparison group related either to the relative efficacy of more than one specified procedure or to patient selection where a specified baseline 'risk factor' was analysed in relation to relative success or failure of the intervention.

(c) A case series was defined as a report of observations based on clinical practice. Such studies may generate hypotheses by post-hoc case comparisons.

(d) For randomized trials and cohort studies, Cochrane risk of bias tools were applied [https://methods.cochrane.org/bias/sites/methods.cochrane.org.bias/files/public/uploads/6.%20Assessing%20risk%20of%20bias%20in%20included%20studies%20v1.0%20Standard%20author%20slides.pdf] and used to distinguish between high and low quality RCTs (Oxford level 1b or level 2b) and high- and low-quality cohort studies (Oxford level 2b or level 4). Case control studies were assessed using the National Institutes of Health (NIH) quality assessment tool

[http://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/case-control] (Oxford level 3b or 4).

5.2.8. Summary measures

Results were tabulated by outcome and described with appropriate summary statistics (percentages, means and ranges). For very rare events, the aggregate number and denominator were reported. Quantitative data synthesis was performed for key outcomes using meta-analysis in STATA SE v14. Pooled proportions and means were estimated, permitting exploration of heterogeneity and bias. Where continuous measures failed to report measures of variance these were approximated as range/4. Random effect meta-analytic models were estimated to characterise rates of events and heterogeneity between studies, with sub-grouping by procedure. Where studies did not provide data in a useful summary form, available data were tabulated but not included in the meta-analysis. Results were presented as aggregate means with confidence intervals and graphically displayed within Forest plots. For pooled studies, the I^2 value (reflecting intra-group heterogeneity) was reported and interpreted in accord with published guidance where 0-40% = heterogeneity might not be important, 30%-60% = moderate heterogeneity, 50-70% substantial heterogeneity and 75%-100% = considerable heterogeneity (Higgins 2011). The magnitude and direction of effect, and strength of evidence p-value from the chi-squared test, were used to interpret the importance of heterogeneity.

Evidence within reviews was predominantly provided by observational cohort data with relatively few experimental studies (trials) identified. Consequently, the review analyses all studies as individual cohorts, by procedure, to achieve inclusion and consistency;

pooled findings are compared with the findings of individual trials. Where several trials were identified within a review (e.g. rectal excision procedures) meta-analyses was performed with sub-grouping by procedure and by evidence grade. Findings by evidence grade were reported only when they deviated qualitatively from the overall pooled summary. Given the nature and reporting of data, study-level meta-regression was not attempted.

5.2.9. Risk of bias across studies

Publication bias was assessed for outcomes where meta-analysis was performed. Other limited analysis was performed based on study size, design and publication date where this contributed to interpretation. Subgroup analysis was explored for the main procedural variations.

5.3. Clinical guidance development

5.3.1. Aims

The process had 3 main aims:

(a) Development of summary evidence statements

(b) Development of graded practice recommendations

(c) Development of summary research recommendations

5.3.1.1. Development of summary evidence statements

Summary evidence statements were produced by the Clinical Guidance Group (CGG). This group was convened in summer 2014. A final list of participants was selected primarily from colorectal surgeons, gastroenterologists, urogynaecologists and specialist nurses with a strong interest in functional colorectal and pelvic floor disorders.

This group included senior and junior investigators. Methodological expertise was provided by Professor James Mason (University of Warwick), and NHS Specialised Services stakeholder representation by Mr Mark Chapman. A series of meetings followed (Bristol, November 2014; London, June 2015; Manchester, November 2015; and Edinburgh, July 2016) at which the evolving summary evidence statements (from reviews) were eventually ratified and prototype clinical practice recommendations drafted.

The CGG used 'focus group' methodology to gain consensus by *in silico* and face to face meetings. The number of participants (>12), and 4 rounds of written revisions fulfilled the basic criteria required for a guideline decision group (National Institute for Health and Clinical Excellence, April 2007) and allowed a sufficiently reliable process at an acceptable cost in terms of travel, expenses etc. The heterogeneity of the group (specialty, nationality, expertise) was deemed desirable to be representative of a range of stakeholders. Agreement was defined without 'weighting' of any participant's views, although some participants contributed more than others to the process.

Using the synthesis of the evidence base the group drafted statements of evidence based on best evidence available (which varied significantly by procedure). The clinical guidance group discussed, revised and graded summary statements of evidence level using the Oxford 2009 CEBM system (http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009) (Table 5.3) based on the review of evidence. For clarity, roman numerals (I – IV) were used to denote summary levels of evidence for graded evidence in contrast to Arabic numerals for individual studies, e.g. 1a, 2b etc. Summary levels could apply either positively or negatively to each procedure.

Care was taken to avoid any contamination of expert opinion into statements, these thus solely reflecting summated evidence from systematic review. Some language used in summary evidence statements was deliberately chosen to reflect use of pooled data. Thus, the term 'typical' or 'typically' specifically denotes that data for the event in question have been derived from random effects analysis.

5.3.1.2. Development of graded practice recommendations (GPRs)

This had 2 main stages: (1) development of 'prototype' GPRs by the Clinical Guidance Group, and (2) development of a final GPR list by a European Consensus group.

5.3.1.2.1. Development of prototype GPRs

After a common understanding of the evidence was established, group discussion balanced clinical experience and evidence summaries to arrive at shared judgements about recommendations for care, thus deriving relevant recommendations for decision making in clinical practice. Group processes risk personal bias based on 'eminence' or 'eloquence' if led and supported ineffectively: adequate methodological support in the use of evidence and dialectic was provided to support the process to ensure a balance of views as well as to promote generalizability and impact. This stage embodied summary evidence statements (from each review), data from some excluded level I studies (e.g. RCTs that were excluded for short follow up or published after the review date) (a further search was run by CK on 03.10.16 for the date range 22.02.16 to 03.10.16 including original terms and 'clinical trial') and expert opinion derived from the decision group and selected prior published guidance documents (Oxford 5).

Final grading followed Oxford CEBM recommendations (A-D) (Evans et al. 2014) (Table 5.3]). As with levels of evidence the grades of evidence could apply either positively or negatively to the procedure.

TABLE 5.3 - (A) OXFORD CEBM (2009) SUMMARY LEVELS OF EVIDENCE AND (B) GRADES OF RECOMMENDATION

(A)

Summary level of evidence	Type of studies	Evidence included specific to review	Notes specific to review exclusions
I	High quality RCT All or none study	Oxford 1b, 1c*	1a (SR RCTs) excluded since no secondary research included in systematic review
II	Poor quality RCT Individual high-quality cohort study Ecological study	Oxford 2b 2c*	2a (SR cohort studies) excluded since no secondary research included in systematic review
III	Individual high-quality case-control study	Oxford 3b*	3a (SR case-control studies) excluded since no secondary research included in systematic review
IV	Case series and poor-quality cohort and case-control studies	Oxford 4	The majority of studies included in systematic review
V	Expert opinion, bench research	Oxford 5	Excluded in systematic review

(B)

Grades of recommendation	Evidence required
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolations from level 1 studies
C	Level 4 studies or extrapolations from level 2 or 3 studies
D	Troublingly inconsistent or inconclusive studies of any level (I-IV)
N	Recommendation based on clinical understanding in the absence of evidence †

** No studies of these designs found by search for any procedure; † but where a recommendation was considered necessary to highlight the absence of evidence for an important practice point.*

5.3.1.2.2. Development of final GPRs

The European Consensus group comprised a panel of European experts (colorectal and pelvic floor surgeons) nominated by the European Society of Coloproctology (ESCP). Twenty experts were invited from 10 European countries of whom 18 participated from 9 countries.

Consensus methodology was derived from the RAND/UCLA Appropriateness Method (Prepared for Directorate General XII, European Commission 2001) (Finch K 2001). Prototype Graded Practice Recommendations (derived from the clinical guidance group) were presented (on a spreadsheet) for each procedure under 3 subheadings: 'patient selection', 'procedural considerations' and 'patient counselling'. For each, a number of GPRs were listed, each with associated levels of evidence and grade of prototype recommendation. For each, consensus panellists were asked 'Does this recommendation lead to an expected health benefit that exceeds the expected negative consequences of its introduction?' Examples of health benefits in this context could be improved surgical outcome, improved patient experience, improved functional capacity etc.; the negative consequences could include increased morbidity, anxiety, pain, time lost from work, denial of an investigation or treatment. Panellists were asked to base their judgement on clinical grounds only, i.e. exclusive of financial cost (Brook et al. 1986).

Responses to each listed recommendation used a linear analogue scale of 1-9 to assess views on the benefit-to-harm ratio. Using this scale, a score of 1-3 indicated that they expected the harms of introducing the recommendation to greatly outweigh the expected benefits and a score of 7-9 that the expected benefits greatly outweighed the

expected harms. A middle rating of 4-6 could mean either that the harms and benefits were considered about equal or that the panellist was unable to make a judgement for the recommendation. Panellists were asked to try and provide a response for all listed recommendations.

Responses were analysed in accordance with the first phase of RAND/UCLA guidance, with each recommendation classified as "appropriate," "uncertain" or "inappropriate" according to the panellists' median score and the level of disagreement. Indications with median scores in the 1-3 range were classified as inappropriate, those in the 4-6 range as uncertain, and those in the 7-9 range as appropriate. All indications rated "with disagreement," whatever the median, were classified as uncertain. "Disagreement" here basically implied a lack of consensus, either because of polarisation or spread over the entire scale (defined for a sample of 18 panellists as >5 rating the indication outside the 3-point region [1-3; 4-6; 7-9] (Finch K 2001)). Further phases of consensus following discussion to reduce variation were not conducted.

5.3.1.3. Development of summary research recommendations

One of the initial drivers for this process (NIHR CapaCiTY) was the need to define the main evidence needed for future surgical trials of patients with chronic constipation. During the development of this guidance, some trials have commenced patient recruitment such as CapaCiTY study 3 (RCT of laparoscopic ventral rectopexy). There is however still a great need to define research questions that could inform future UK and international commissioning of research funding. Research recommendations have been attributed a priority (high, medium or low) based on the expert opinion of the current working group and may help inform discussion about future funding priorities.

5.4 Scope

Herein we report the outcomes of rectal suspension procedures in adults presenting with chronic constipation symptoms. In effect, this is however limited to patients with obstructed defaecation and internal prolapse (intussusception). Procedures considered beyond the scope of systematic review included rectal excisional procedures, e.g. stapled transanal rectal resection (STARR) (Biviano et al. 2011), rectal reinforcement procedures, e.g. transanal/transperineal repair of rectocoele (Hirst et al. 2005), and less common variant of suspension procedures, e.g. laparoscopic promonto-fixation (Sabbagh et al. 2010). Studies where outcomes could not be segregated by eligible procedure were also excluded due to a mixed patient population with internal and external rectal prolapse (Sitzler et al. 1998, Bruch et al. 1999, Schultz et al. 1999, Badrek-Amoudi et al. 2013, Laubert et al. 2013, Mackenzie and Dixon 2014, Owais et al. 2014, Gravie and Maigne 2015), mixed indications including numerous pelvic floor abnormalities (Gultekin et al. 2015) or limited post-operative outcomes (Abet et al. 2012).

5.5 Previous reviews

Seven systematic (Samaranayake et al. 2010, Cadeddu et al. 2012, Rondelli et al. 2014, Faucheron et al. 2015, Gouvas et al. 2015, Ramage et al. 2015, Tou et al. 2015) and 4 narrative (Senagore 2003, Harmston and Jones 2011, Cullen et al. 2012, Shastri-Hurst and McArthur 2014) reviews have focused on the outcome of rectal suspension. Of the systematic reviews, 3 focused on full thickness external rectal prolapse (Cadeddu et al. 2012, Faucheron et al. 2015, Gouvas et al. 2015), 2 included both full-thickness prolapse

and constipation participants (Samaranayake et al. 2010, Tou et al. 2015), and 2 analysed outcomes of robotic surgery (Rondelli et al. 2014, Ramage et al. 2015).

5.6 Summary of search results and study quality

The search yielded a total of 47 manuscripts for full text review (Figure 5.1).

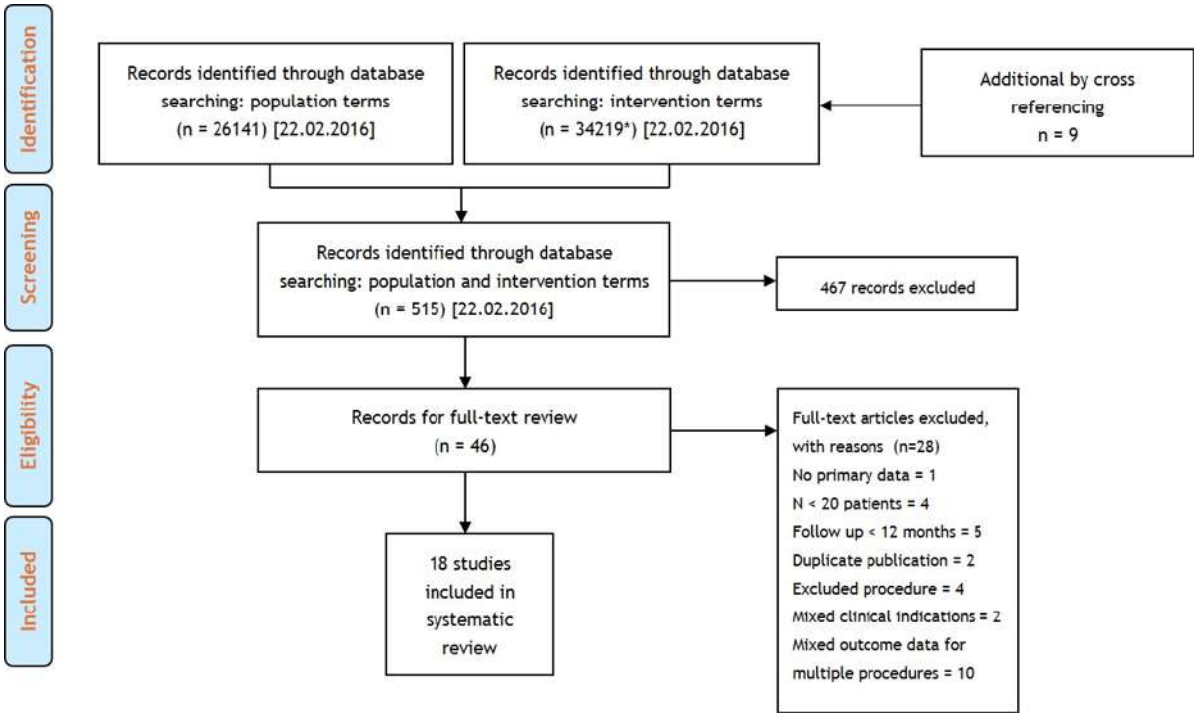

FIGURE 5.1 - PRISMA DIAGRAM OF SEARCH RESULTS.

From these, 18 articles published between 1995 and 2015 contributed to the systematic review, providing data on outcomes in a total of 1238 patients (range 20-233 patients per study) based on 18 defined patient cohorts (Table 5.4). Specific exclusions after full-text review (and after exclusion of non-English language publications) included 4 studies where the population sample was confirmed to be less than 20 patients (Orrom et al. 1991, Graf et al. 1996, Tweedie and Varma 2005, van den Esschert et al. 2008), 4 studies of out-of-scope procedures (Hirst et al. 2005, Portier et al. 2006, Sabbagh et al. 2010,

Biviano et al. 2011), 2 studies where data were considered a duplicate (Johnson et al. 2003, Evans et al. 2014), and 10 studies where outcomes could not be segregated by eligible procedure (Sitzler et al. 1998, Bruch et al. 1999, Schultz et al. 1999, Abet et al. 2012, Badrek-Amoudi et al. 2013, Laubert et al. 2013, Mackenzie and Dixon 2014, Owais et al. 2014, Gravie and Maigne 2015, Gultekin et al. 2015). Other exclusion criteria were: constipation not representing an indication (n=2) (Lahr et al. 1999, Maggiori et al. 2013), follow-up less than 12 months (n=5) (Schultz et al. 1996, Silvis et al. 1999, Schultz et al. 2000, Wong et al. 2011, Johnson et al. 2012), and lack of primary patient data (one international survey on 391 surgeons) (Formijne Jonkers et al. 2013).

TABLE 5.4 - ALL STUDIES INCLUDED IN SYSTEMATIC REVIEW.

Author	Year	Centre	Country	Total N	FU*	Design	Level†
van Tets	1995	Groot	Netherlands	37	72	RCS	IV
Tsiaoussis	2005	Heraklion	Greece	27	45	PCH	IV
Vermeulen	2005	Rotterdam	Netherlands	20	18	RCS	IV
Von Papen	2006	Herston	Australia	56	44	PCS	IV
Collinson	2009	Oxford	UK	75	12	PCS	IV
Kargar	2011	Shaid Sadoughi	Iran	39	32	RCS	IV
Portier	2011	Toulouse	France	40	22	PCS	IV
Wong	2011	Nantes	France	41	12	PCH	IIB
Wong	2011	Nantes	France	84	29	PCH	IV
Sileri	2012	Rome	Italy	34	12	PCS	IV
Wahed	2012	Gateshead	UK	65	12	PCS	IV
Evans	2013	Oxford	UK	30	36	PCS	IV
Formijne Jonkers	2013	Amersfoort	Netherlands	233	30	RCS	IV
Gosselink	2013	Oxford	UK	151	12	RCS	IV
Mantoo	2013	Nantes	France	128	16	PCH	IIB

Borie	2014	Montpellier	France	52	18	RCS	IV
Franceschilli	2015	Rome	Italy	100	20	PCS	IV
Tsunoda	2015	Kamogawa City	Japan	26	16	PCS	IV

**Mean follow-up in months; †Oxford CEBM (Evans et al. 2014). A median follow-up time was not provided. PCH: prospective cohort study; RCS: retrospective case series; PCS: prospective case series study.*

The general quality of studies was poor due to inadequate description of methods. The 18 included studies were all observational with no randomised controlled trials. These comprised two good quality prospective cohort studies (level IIB) (Wong et al. 2011, Mantoo et al. 2013) and 16 (level IV) studies comprising 2 poor quality case-control studies (Evans et al. 2014, Tsunoda et al. 2015), 8 prospective case series (Tsiaoussis et al. 2005, von Papen et al. 2007, Collinson et al. 2010, Portier et al. 2011, Wong et al. 2011, Sileri et al. 2012, Wahed et al. 2012, Franceschilli et al. 2015), and 6 retrospective case series (Vantets and Kuijpers 1995, Vermeulen et al. 2005, Kargar et al. 2011, Formijne Jonkers et al. 2013, Gosselink et al. 2013, Borie et al. 2014). Mean patient follow-up ranged from 12 to 72 months (median 25 months). Fifteen studies derived from European centres, with one each from Australia, Iran and Japan.

5.7 Perioperative data

Perioperative data were reported by all 18 studies (Table 5.5). Reporting of procedure duration was inconsistent but median procedural duration for laparoscopic ventral mesh rectopexy (LVMR) was 159 (range 75-198) minutes; for robotic ventral mesh rectopexy (RVMR), 205 (range 191-218) minutes; for laparoscopic resection rectopexy (LRR), 123 minutes (Wong et al. 2011, Mantoo et al. 2013). Although robotic procedures appeared to take longer, substantial non-reporting of other procedures precluded a clear finding. The two papers on RVMR were from the same centre. It is interesting to

note a decrease in duration of operation, which may indicate a learning curve. Conversion to laparotomy was rare (median 2%, range 0-8%) (Table 5.5), with the most common reason being adhesions. The median length of stay (LOS) was similar for procedures: LVMR, median 3.3 (range 1.0- 7.1) days; RVMR, median 4.3 (range 4.0-4.6) days (data from one centre via two reports) (Wong et al. 2011, Mantoo et al. 2013); LRR, 4 days (data from one study) (von Papen et al. 2007). LOS possibly reflected local policy rather than clinical need, since day case procedures have been shown to be feasible (George et al. 2013, Powar et al. 2013). The reason to keep patients in hospital for up to one week was not documented. Only one paper commented on LOS after open rectopexy (OR) (8.5 days) (Vermeulen et al. 2005).

5.5.1. Summary evidence statements: perioperative data

- Procedures are reported to take from 1.5 to 3.5 hours, with consequent typical LOS of 4-5 days (level IV).
- There was no clear variation between procedures in perioperative measures, although non-reporting by studies may have concealed differences (level IV).

TABLE 5.5 - PERIOPERATIVE DATA BY PROCEDURE.

(A) LAPAROSCOPIC VENTRAL MESH RECTOPEXY (LVMR)

Author	Year	N	Duration, mins	LOS	Total cx, %	Re-op. %	Mesh cx. %	Conv. %	Stoma %	Mort. %
Collinson	2009	75	NR	2	4	0	0	1.3	0	0
Kargar	2011	39	NR	NR	NR	NR	NR	NR	NR	NR
Portier	2011	17 (40*)	NR	NR	7.5	0	0	NR	0	0
Wong	2011	25	159	4.6	NR	0	0	8	0	0
Wong	2011	84	NR	5	8.3	1.2	1.2	3.6	0	0
Sileri	2012	34	110	2	23.5	2.9	0	0	0	0
Wahed	2012	65	NR	2	7.6	1.5	0	1.5	0	0
Formijne Jonkers	2013	233	NR	5	4.7	0.4	0.9	2.5	0.4	0
Gosselink	2013	151	NR	NR	NR	NR	NR	NR	NR	NR
Mantoo	2013	74	163	5	11	0	0	4	0	0
Borie	2014	25	NR	7.1	24	0	NR	8	0	0
Evans	2015	30	NR	NR	10	0	3.4	NR	0	0
Franceschilli	2015	100	75	2	16	1	0	1	0	0
Tsunoda	2015	26	198	1	7.6	0	0	0	0	0

(B) ROBOTIC VENTRAL MESH RECTOPEXY (RVMR)

Author	Year	N	Duration, mins	LOS	Total cx, %	Re-op. %	Mesh cx, %	Conv. %	Stoma %	Mort. %
Wong	2011	16	218	4.6	10.5	0	0	6.3	0	0
Mantoo	2013	44	191	4	0	0	0	5	0	0

(C) LAPAROSCOPIC RESECTION RECTOPEXY (LRR)

Author	Year	N	Duration, mins	LOS	Total cx, %	Re-op. %	Mesh cx, %	Conv. %	Stoma %	Mort. %
Tsiaoussis	2005	23 (27)‡	NR	NR	22	NR	NA	NR	NR	0
Von Papen	2007	56	123	4	13	7	0	2	0	0

(D) OPEN RECTOPEXY (OR)

Author	Year	Operation	N	Duration, mins	LOS	Total cx, %	Re-op. %	Mesh cx, %	Conv. %	Stoma %	Mort. %
van Tets	1995	Posterior mesh rectopexy	37	NR	NR	NR	NR	NR	NA	NR	NR
Vermeulen	2005	Anterior mesh rectopexy	20	NR	8.5	15	0	0	NR	0	0
Portier	2011	Anterior mesh rectopexy	23 (40)*	NR	NR	7.5	0	0	NR	0	0

*LOS: length of stay; Cx: complications; Re-op.: reoperation; Conv.: conversion; Mort.: mortality; NR: not reported. *17 were laparoscopic, 23 open; ‡ 4 open.*

5.6. Harms

There was a considerable heterogeneity in surgical morbidity reported as well as in overall procedural complication rates (Figure 5.2), with individual study rates varying from 0.0% to 23.5% (Table 5.5).

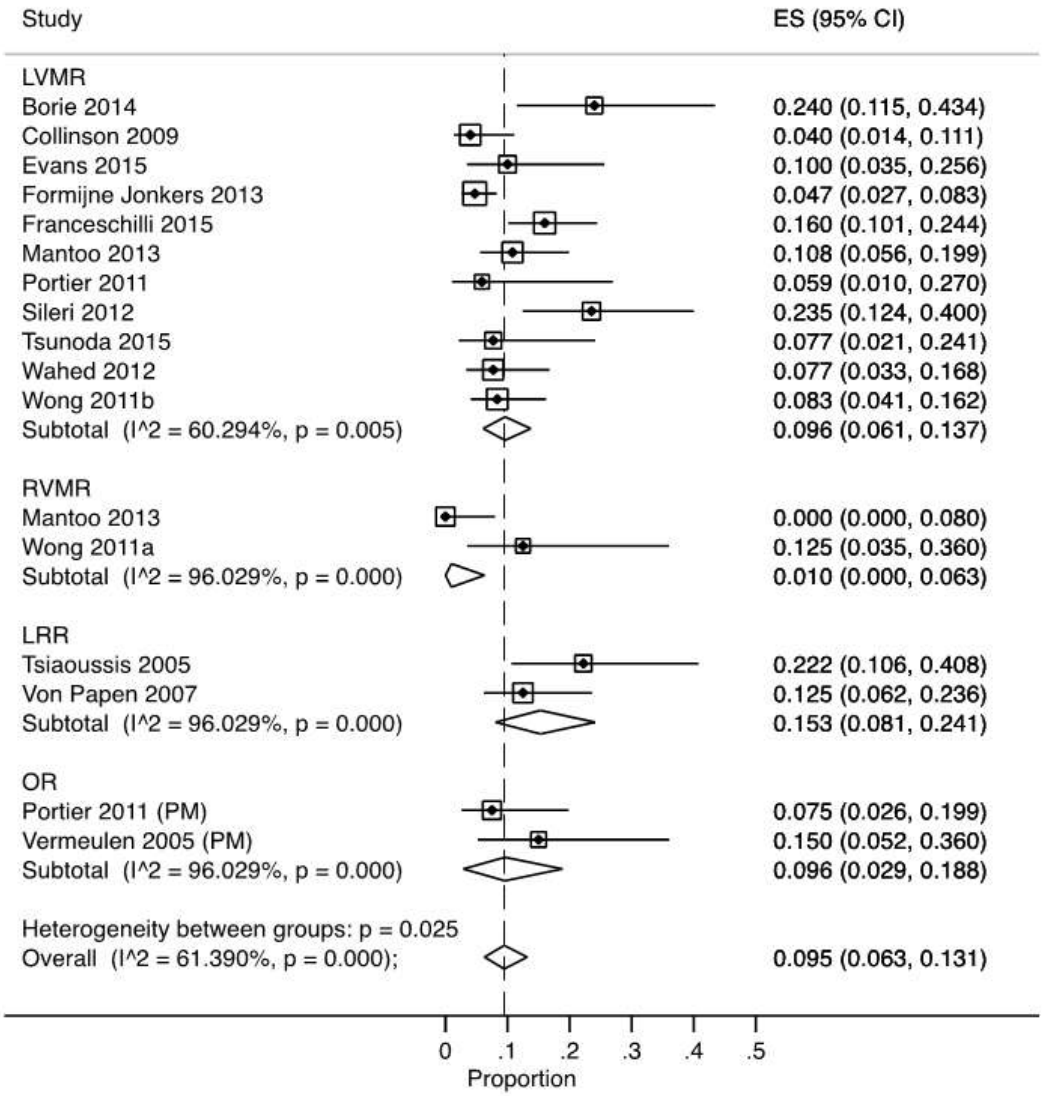

FIGURE 5.2 - FOREST PLOT SHOWING RATES OF TOTAL PROCEDURAL COMPLICATIONS (PERCENTAGE OF PATIENTS) AFTER RECTOPEXY BY PROCEDURE TYPE. KEY: LVMR = LAPAROSCOPIC VENTRAL MESH RECTOPEXY; RVMR = ROBOTIC VENTRAL MESH RECTOPEXY; LRR = LAPAROSCOPIC RESECTION RECTOPEXY; OR = OPEN RECTOPEXY.

Such heterogeneity may reflect different inclusion, thresholds or conventions for recording complications. Complications typically occurred in about 5-15% of patients. Pooled findings suggest that LRR might be associated with higher morbidity (total complications 15% for LRR vs. 10% LVMR) although the findings were not statistically

significant (Z-test, P=0.30), and absolute patient numbers were small for LRR. The majority of complications were minor and included urinary tract infections (the most common reported), wound infections, haematoma formation, persistent pain and urinary retention. There were some more serious complications including port-site hernia, small bowel obstruction (usually after conversion but also related to mesh or suture adhesions), osteomyelitis and bladder injury (often when associated to bladder prolapse surgery). Specific mesh complication rates were rare, with only 5 occurrences after 939 procedures (0.53%). Overall, procedures were safe: conversion to laparotomy was rare (median 2%, range 0-8%) (Table 5.5), with the most common reason being adhesions; stoma was only reported in one study; no perioperative deaths were reported. Two open rectopexy procedures (posterior mesh) were described, but data concerning post-operative complications were limited. There was no mortality recorded after any resuspension procedures.

5.6.1. Summary evidence statements: harms

- Data on harms were inconsistently reported and heterogeneous, making estimates of harm tentative and imprecise (level IV).
- Complications typically occurred in about 5-15% of procedures (level IV).
- Mesh complications were reported in a minority of studies and occurred in about 0.5% (range 0-3.9%) of patients overall (level IV).
- No mortality was recorded after any resuspension procedure, in a total of 1044 patients reporting this outcome (level IV).

5.7. Efficacy

Measurement of clinical outcomes was inconsistent and included the variable use of validated and un-validated scoring instruments for symptoms, such as Patient Assessment of Constipation-Quality of Life (PAC-QOL) and Patient Assessment of Constipation-Symptoms (PAC-SYM) scores (one study only) (Gosselink et al. 2013), Cleveland Clinic Constipation score (Collinson et al. 2010, Wong et al. 2011, Sileri et al. 2012, Formijne Jonkers et al. 2013, Evans et al. 2014, Franceschilli et al. 2015, Tsunoda et al. 2015), obstructed defaecation syndrome (ODS) score (Wong et al. 2011, Formijne Jonkers et al. 2013, Mantoo et al. 2013, Borie et al. 2014), Knowles-Eccersley-Scott score (KESS) (Collinson et al. 2010), Cleveland Clinic Incontinence score (Portier et al. 2011, Formijne Jonkers et al. 2013, Mantoo et al. 2013), Faecal Incontinence Severity Index (FISI) (Collinson et al. 2010, Sileri et al. 2012, Wahed et al. 2012, Formijne Jonkers et al. 2013, Gosselink et al. 2013, Borie et al. 2014, Franceschilli et al. 2015, Tsunoda et al. 2015), and St Marks Incontinence score (Collinson et al. 2010). Global 'success' or 'satisfaction' ratings (GSR) were obtained via a variety of methods in 7 studies (where 'satisfied' or 'very satisfied', 'good', 'very good', and 'excellent' were interpreted as a positive outcome or overall improvement). Further studies also reported individual symptoms. No study reported acquiring data objectively using personnel not involved in the surgical care of the patient or data collection blinded to intervention status. Average reported studies follow-up was 31 months (range 12-72 months).

Accepting these methodological limitations, several reports assert that most patients undergoing rectal suspension procedures were satisfied. Meta-analysis of studies reporting a summary measure found considerable heterogeneity, which may reflect

variation in measurements, patients or procedures. Overall improvement (a good or satisfactory outcome) was reported in 83% (95%CI: 74%-91%, I^2=77%) of cases, based on 328 patients (Table 5.6; Figure 5.3). Similar levels of improvement were recorded for LVMR and OR; only one small study reported improvement after LRR, and data were not available for RVMR.

TABLE 5.6 - OVERALL IMPROVEMENT BASED ON GLOBAL SATISFACTION RATINGS (GSR)

(A) LAPAROSCOPIC VENTRAL MESH RECTOPEXY (LVMR)

Author	Year	Follow up (months)	N	% success
Collinson	2009	12	75	NR
Kargar	2011	22	39	74
Portier	2011	32	40 (17*)	97
Wong	2011	12	25	NR
Wong	2011	29	84	NR
Sileri	2012	12	34	NR
Wahed	2012	12	65	71
Formijne Jonkers	2013	30	233	NR
Gosselink	2013	12	151	NR
Mantoo	2013	16	74	NR
Borie	2014	NA	25	NR
Evans	2015	36	30	NR
Franceschilli	2015	20	100	89
Tsunoda	2015	16	26	NR

(B) ROBOTIC VENTRAL MESH RECTOPEXY (RVMR)

Author	Year	Follow up (months)	N	% success
Wong	2011	12	16	NR
Mantoo	2013	16	44	NR

(c) Laparoscopic resection rectopexy (LRR)

Author	Year	Follow up (months)	N	% success
Tsiaoussis	2005	45	23 (27)‡	93
Von Papen	2007	44	56	NR

d) Open rectopexy (OR)

Author	Year	Operation	Follow up (months)	N	% success
van Tets	1995	Posterior mesh rectopexy	72	37	70
Vermeulen	2005	Anterior mesh rectopexy	18	20	63
Portier	2011	Anterior mesh rectopexy	22	40 (23*)	97

*Cx: complications; NR: not reported. * 17 were laparoscopic, 23 open; ‡ 4 open.*

The initial aim of 'suspension' procedures is to treat symptoms. Functional assessment of constipation is therefore the most important outcome. However, many patients also suffer from incontinence, typically post-defaecatory seepage. The various scoring instruments and functional outcomes employed are reported in Table 5.7. Generally, measures are too sparsely reported to be informative. For LVMR, Cleveland Clinic Constipation score improved from a median of 14 (range 7-18) to a median of 5 (range 4-7) in 6 studies providing pre- and post-operative data. Improvement in constipation was highly heterogeneous and only reported in a minority of studies, varying from 20% to 97%. By pooling data for LVMR, the reported improvement in constipation was 86% (95%CI: 20-97%).

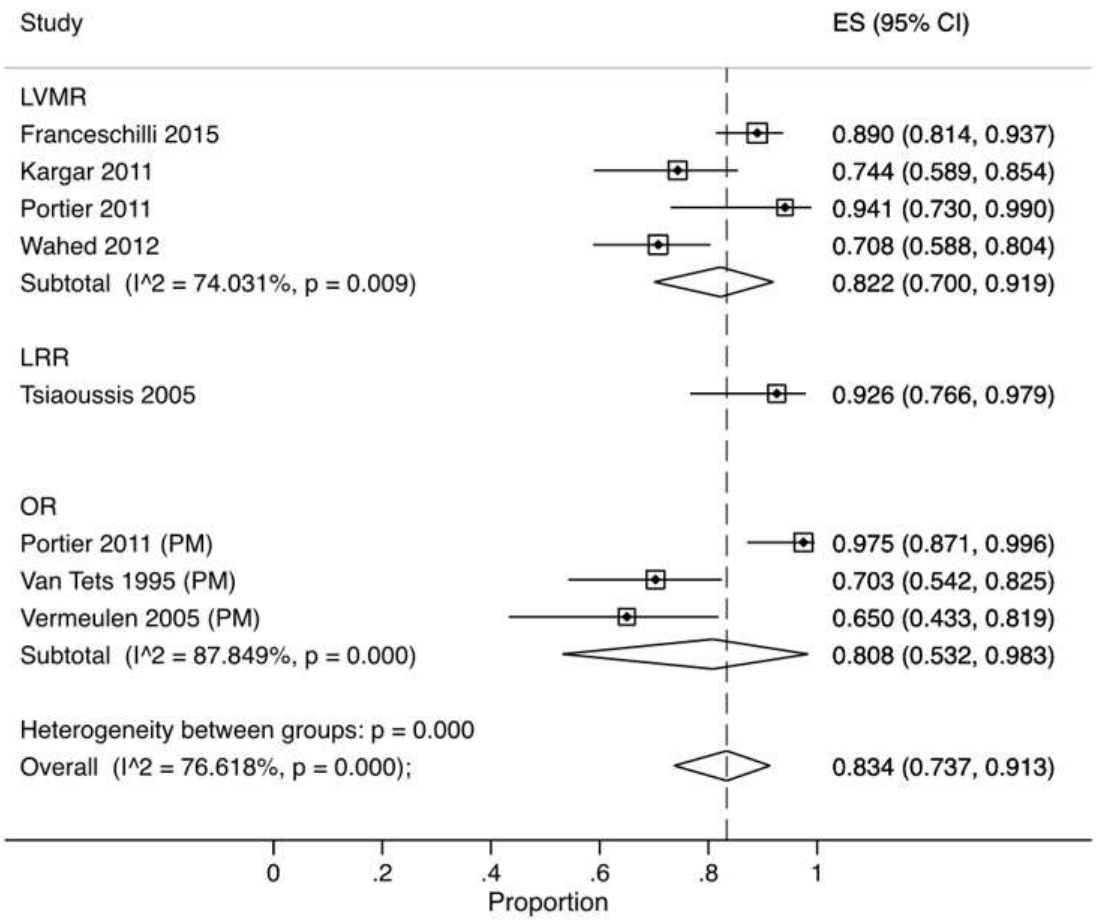

FIGURE 5.3 - FOREST PLOT SHOWING RATES OF OVERALL IMPROVEMENT (PERCENTAGE OF PATIENTS) AFTER RECTOPEXY BY PROCEDURE TYPE. KEY: LVMR = LAPAROSCOPIC VENTRAL MESH RECTOPEXY; LRR = LAPAROSCOPIC RESECTION RECTOPEXY; OR = OPEN RECTOPEXY.

While the clinical outcome has primacy, the most immediate visible consequence of surgery is to correct anatomy. Therefore, an assessment of anatomical recurrence is also important (although necessarily representing only a surrogate outcome). Anatomical recurrence rates varied between 0-21% (Figure 5.4), but typically occurred in 2-7% of patients in most studies. Functional outcome data on robotic surgery and LRR were rarely available, but again anatomical correction was very likely achieved with both procedures. No conclusions about functional or anatomical outcomes could be made for the other rectopexy procedures.

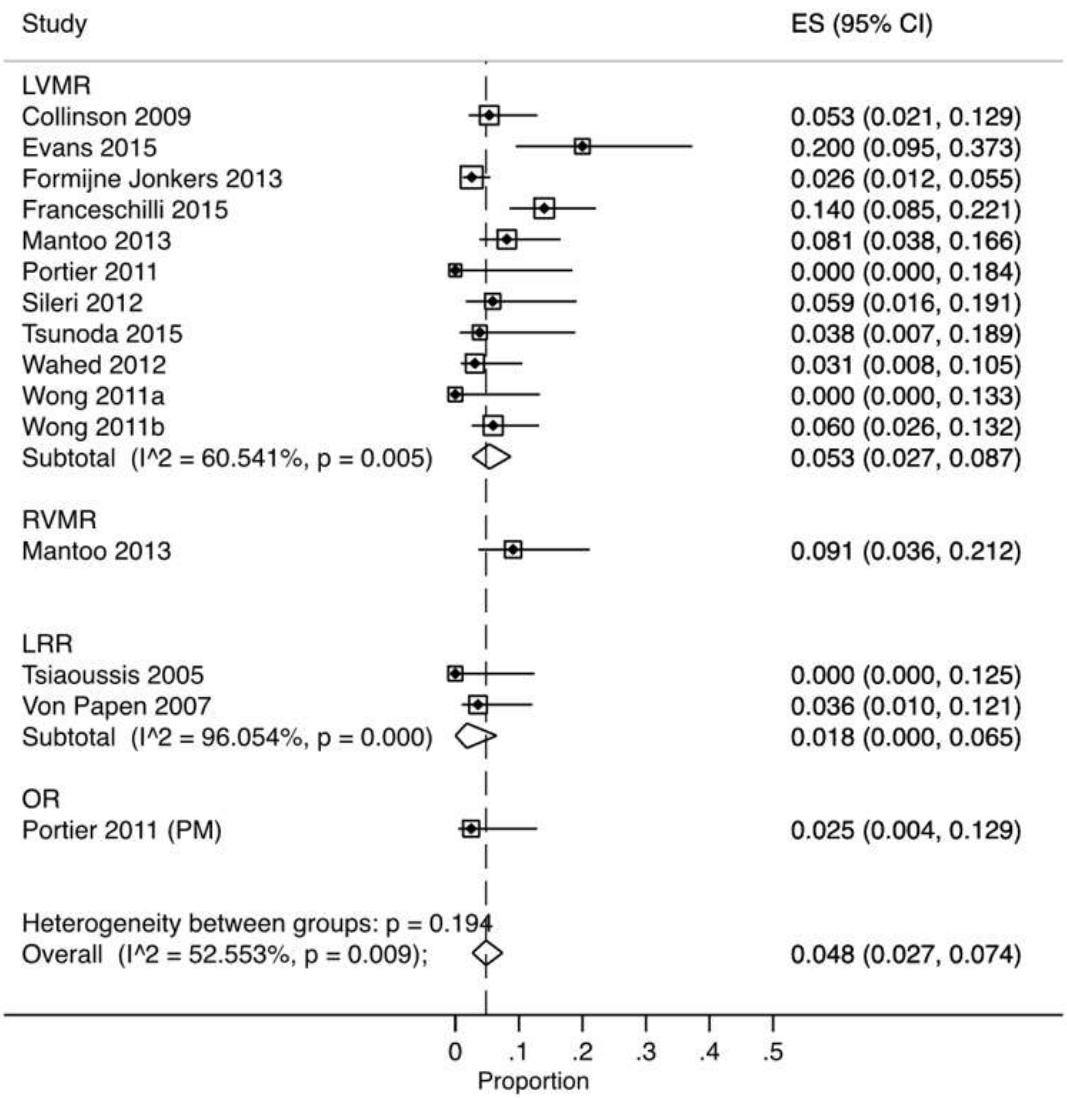

FIGURE 5.4 - FOREST PLOT SHOWING RATES OF ANATOMICAL RECURRENCE (PERCENTAGE OF PATIENTS) AFTER RECTOPEXY BY PROCEDURE TYPE. KEY: LVMR = LAPAROSCOPIC VENTRAL MESH RECTOPEXY; RVMR = ROBOTIC VENTRAL MESH RECTOPEXY; LRR = LAPAROSCOPIC RESECTION RECTOPEXY; OR = OPEN RECTOPEXY.

TABLE 5.7 - FUNCTIONAL AND CLINICAL OUTCOMES BY PROCEDURE

(A) LAPAROSCOPIC VENTRAL MESH RECTOPEXY (LVMR)

Author	Year	N	CCS pre	CCS post	ODS pre	ODS post	FISI pre	FISI post	Constipation improved %	Anatomical recurrence %
Collinson	2009	75	12	5	NR	NR	28	8	86	5
Kargar	2011	39	NR	NR	NR	NR	NR	NR	NR	NR
Portier	2011	40	NR	NR	NR	NR	NR	NR	worse	2.5
Wong	2011	25	NR	NR	NR	NR	NR	NR	NR	0
Wong	2011	84	7	5	NR*	NR*	NR	NR	Improved	6.3
Sileri	2012	34	16	7	NR	NR	9	3	NR	5.9
Wahed	2012	65	NR*	NR*	NR	NR	NR*	NR*	97	3.7
Formijne Jonkers	2013	233	NR	8.1	NR*	NR*	NR*	NR*	81	2.6
Gosselink	2013	151	NR	NR	NR	NR	NR*	NR*	NR	NR
Mantoo	2013	74	NR	NR	NR †	NR †	NR	NR	NR	8
Borie	2014	25	NR	NR	16	7.6	24	2	20	NR
Evans	2015	30	17	6	NR	NR	19	NR	NR	21
Franceschilli	2015	100	18.4	5.5	NR	NR	NR*	NR*	89	14
Tsunoda	2015	26	11	4	NR	NR	30	6	NR	3.8

(B) ROBOTIC VENTRAL MESH RECTOPEXY (RVMR)

Author	Year	N	CCS pre	CCS post	ODS pre	ODS post	FISI pre	FISI post	Constipation improved %	Anatomical recurrence %
Wong	2011	16	NR	NR	NR	NR	NR	NR	NR	NR
Mantoo	2013	44	NR	NR	NR	NR	NR	NR	NR †	8

(C) LAPAROSCOPIC RESECTION RECTOPEXY (LRR)

Author	Year	N	CCS pre	CCS post	ODS pre	ODS post	FISI pre	FISI post	Constipation improved %	Anatomical recurrence %
Tsiaoussis	2005	23 (27)‡	NR	NR	NR	NR	NR	NR	NR	0
Von Papen	2007	56	NR	NR	NR	NR	NR	NR	53	3.6

(D) OPEN RECTOPEXY (OR)

Author	Year	Operation	N	CCS pre	CCS post	ODS pre	ODS post	FISI pre	FISI post	Constipation improved %	Anatomical recurrence %
van Tets	1995	Posterior mesh rectopexy	37	NR	NR	NR	NR	NR	NR	NR	NR
Vermeulen	2005	Anterior mesh rectopexy	20	NR	NR	NR	NR	NR	NR	NR	NR
Portier	2011	Anterior mesh rectopexy	40 (23º)	NR	NR	NR	NR	NR	NR	worse	2.5

*NR: not reported; CCS: Cleveland Clinic Constipation score; ODS: obstructed defaecation syndrome score; FISI: Faecal Incontinence Severity Index; * significant improvement (no data given); † decreased or improved but not significantly (no data given); ‡ 4 open; º 23 open procedures.*

5.7.1. Summary evidence statements: efficacy

- Data on efficacy were inconsistently reported and findings heterogeneous, making estimates tentative and imprecise (level IV).
- Although inconsistent, patient GSR suggest that a good or satisfactory outcome typically occurs in 83% (74-91%) of patients (level IV).
- Similar levels of satisfaction were recorded for all procedures where data were available (LVMR, OR, LRR) (level IV).
- Patient-reported improvements in constipation occurred in 86% (95%CI: 20-97%) of patients after LVMR (level IV).

- Limited evidence found consistently improved Cleveland Clinic Constipation scores for patients undergoing LVMR (level IV).
- Anatomical recurrence typically occurred in about 2-7% of patients (level IV).

5.8. Patient selection

Patient selection is perceived by many experts as extremely important when choosing the surgical approach. Whilst these procedures may be efficient at correcting normal anatomy (median 95%, range 79-100%), many underlying functional and organic pathologies may jeopardize the success of surgery in the attempt of 'curing' the patient (Pescatori et al. 2007). Fifteen of 18 papers highlight the fact that all patients had undergone a period of conservative management. Other than this common feature, selection was inconsistent. Even the diagnosis of abnormal anatomy varied throughout the literature. Studies described interventions for patients with: ungraded intussusception (Vermeulen et al. 2005, von Papen et al. 2007); 'rectoanal' intussusception (Tsiaoussis et al. 2005, Tsunoda et al. 2015); 'high grade' intussusception (Gosselink et al. 2013); 'grade 3 or 4' intussusception (Collinson et al. 2010, Portier et al. 2011, Sileri et al. 2012, Formijne Jonkers et al. 2013, Franceschilli et al. 2015); 'anterior or circumferential' intussusception (Vantets and Kuijpers 1995); rectocoele +/- intussusception or +/- cystocoele (Vermeulen et al. 2005, Wahed et al. 2012, Borie et al. 2014); complex rectocoele of above 2-3 cm (Wong et al. 2011); multi-compartment pelvic floor disorders (Mantoo et al. 2013); solitary rectal ulcer syndrome (SRUS) (Kargar et al. 2011, Evans et al. 2014). Thus, it was difficult to draw any conclusions as to which group could benefit from intervention. When summarising the data, the most common theme regarding patient selection is a high-grade

intussusception (i.e. rectoanal or Oxford grade ≥3). Table 5.8 lists the papers where this inclusion criterion has been adopted and one of the primary indications along with a summary of the outcome measures reported (if given in more than one paper). The conclusions from this sub-analysis resemble those described in the whole review.

SRUS deserves specific mention as two papers included patients specifically diagnosed with this condition (Kargar et al. 2011, Evans et al. 2014). Patients report passage of mucus and bloody liquid on defaecation, with an ulcer seen within the rectum. Treatment is conservative, initially using biofeedback and behavioural intervention. A proportion of patients present an element of internal intussusception, which may reflect the ulcerated area as the apex of the intussusception, repetitively traumatised with straining. The surgical correction of a prolapse (when detected) may be reasonable in the hope of resolving the ulcer. Data on a total of 75 patients with SRUS who have undergone LVMR are available from the two papers. Healing of the ulcer occurred in 78% of patients after surgery.

TABLE 5.8 - SUMMARY OF PAPERS WHERE PARTICIPANTS HAD A HIGH-GRADE INTERNAL INTUSSUSCEPTION (RECTOANAL, OXFORD GRADE 3 OR 4)

Author	Year	Op	N	FU	% success	CCS pre	CCS post	FISI pre	FISI post	Constipation improved	Anatomical recurrence
Tsiaoussis	2005	**	27	45	93	NR	NR	NR	NR	NR	0
Collinson	2009	LVMR	75	12	NR	12	5	28	8	86	5
Portier	2011	*	40	22	97	NR	NR	NR	NR	worse	2.5
Wong	2011	***	41	12	NR	NR	NR	NR	NR	NR	6.3
Sileri	2012	LVMR	34	12	NR	16	7	9	3	NR	5.9
Formijne Jonkers	2013	LVMR	233	30	NR	8.1	NR	NR	NR	NR	2.6
Gosselink	2013	LVMR	151	12	NR	NR	NR	NR	NR	NR	NR
Borie	2014	LVMR	52	1-18	NR	NR	NR	24	2	20	NR
Evans	2015	LVMR	30	36	NR	17	6	19	NR	NR	21
Franceschilli	2015	LVMR	100	20	89	18.4	5.5	NR	NR	89	14
Tsunoda	2015	LVMR	26	16	NR	11	4	30	6	NR	3.8

** Lap and Open Ant mesh rectopexy; ** Lap resection rectopexy; *** LVMR and RVMR.*

5.8.1. Summary evidence statements: patient selection

- Although patient selection is perceived as vital in predicting outcome, it was inconsistently documented (level IV).
- One common indication appears to be high grade rectal intussusception (level IV).
- For high grade intussusception, LVMR, RVMR and resection rectopexy typically correct anatomy in about 80-100% of cases (level IV).
- If SRUS is associated with prolapse, a LVMR typically results in healing of the ulcer in around 80% of patients (level IV).

5.9. Graded practice recommendations

Table 5.9 shows all GPRs proposed by the clinical guideline group for rectal suspension procedures. The outcomes of the consensus process have been presented as median score (1-9) and by classification based on RAND-UCLA methodology: appropriate; uncertain and inappropriate. The reader is reminded that appropriateness is not directly extrapolated from the median score but rather the overall data distribution (see paragraph 5.2).

TABLE 5.9 - GRADED PRACTICE RECOMMENDATIONS

Rectal suspension procedures	**Evidence level**	**Grade**	**Median score**	**Decision**
Patient selection				
1. Rectal suspension procedures should be considered only for patients failing appropriate non-surgical treatments	IV	D	9	Appropriate
2. Rectal suspension procedures should be considered for patients with the following anatomical abnormalities in conjunction with symptoms suggestive of rectal evacuation disorder				
• High grade intussusception (recto-anal e.g. Oxford grade: 3-5)	IV	C	8	Appropriate
• SRUS with associated intussusception	IV	C	8	Appropriate
3. Diagnosis of anatomical abnormalities should be conducted to a standard where agreement exists that observed findings can be deemed pathological based on appropriate normative data (derived within the department or derived elsewhere but using identical methodology e.g. for defaecographic imaging)	V	N	8	Appropriate
4. Given concerns regarding outcome, the following should be regarded as relative contraindications to rectal suspension procedures				
• Significant psychiatric disorders	V	N	7	Appropriate
• Significant chronic pain syndromes including IBS	V	N	8	Appropriate
• Morbid obesity	V	N	8	Appropriate
• Known hostile abdomen / pelvis	V	N	8	Appropriate
• Joint hypermobility syndrome (EDS3) / connective tissue disorders	V	N	5	Uncertain
5. Patients considered for rectal suspension procedures should have specialist multidisciplinary discussion	V	N	8	Appropriate
6. In view of need for specialist investigations and review, patients should only undergo rectal suspension procedures for constipation in centres with access to appropriate specialist services	V	N	8	Appropriate
7. Rectal suspension procedures (especially those employing mesh) require special consideration in women who plan to become pregnant	V	N	8	Appropriate
Procedural considerations				

1.	There is insufficient current evidence to conclude that any one rectal suspension procedure is clearly superior to another	IV	C	7	Appropriate
2.	Laparoscopic surgery should be considered in suitable patients because of:				
	• Cosmesis and other generally perceived benefits such as reduced incisional hernia	V	N	8	Appropriate
	• Possible reduction in adhesion formation	V	N	8	
	• Superior access to the deep pelvis	V	N	7	Appropriate Appropriate
3.	There is no current evidence to suggest superiority of robotic surgery over a standard laparoscopic approach	IV	D	8	Appropriate
4.	Careful consideration should be given to the type of mesh and fixation	V	N	8	Appropriate
Patient counselling					
1.	Approximately 83% (73-91%) patients report some benefit at follow up greater than 1 year after rectal suspension procedures	IV	C	8	Appropriate
2.	Total perioperative complication rates vary greatly but may occur in approximately 5-15% of patients regardless of procedure choice	IV	C	8	Appropriate
3.	Serious complications such as mesh erosion occur in 0-4% of patients however no mortality has not been reported	IV	C	8	Appropriate
4.	The effect on constipation symptoms is highly variable and data are only available for LVMR after which most patients (86%) report an improvement in constipation symptoms	IV	C	7	Appropriate
5.	In patients with SRUS, ulcer healing is observed in 78% of patients	IV	C	8	Appropriate

Chapter 6 - Outcome of laparoscopic ventral mesh rectopexy for intussusception: a retrospective cohort study of 537 patients with independent data analysis

6.1. Supervisors Introduction

This chapter contains data that were sent to our unit for independent analysis from Mr Tony Dixon. The data derive from patients who had undergone surgery at the North Bristol NHS Trust and Spire Hospital Bristol. These data were collected prospectively by a number of research fellows between 1999 and 2016. At the time of receipt of these data, the subsequent medico-legal issues and widespread media coverage were not known, and Dr Grossi analysed these data in good faith under my supervision. While we have decided (on advice from the Association of Coloproctology Great Britain and Ireland) not to publish these data, I do believe these data to be a true record of outcomes (and I have supplied this opinion in writing to authorities investigating conduct in Bristol). Further, regardless of the veracity of the data or contention around the subject, I believe that neither detract from the intellectual exercise of Dr Grossi in cleaning, analysing and writing up these data for publication. I therefore believe that these are appropriate doctoral content.

Professor Charles Knowles

6.2. Introduction

Dynamic structural abnormalities of the anorectum and pelvic floor can cause symptoms of obstructed defaecation (Mellgren et al. 1994) and faecal incontinence (Collinson et al. 2009) and affect a large subgroup of patients with chronic constipation (Dvorkin et al. 2005). The most common abnormalities (either singly or together) are rectocoele and intussusception (Mellgren et al. 1994). While parameters for diagnosis and intervention vary (Shorvon et al. 1989, Marti et al. 1999, Collinson et al. 2009), most would agree that large functional rectocoeles and high grade intussuscepta (i.e. those descending to the level of anal canal or beyond (Collinson et al. 2009)) may benefit from some form of surgical intervention in well-selected patients. Procedures used to surgically correct these abnormalities include those that reinforce the rectovaginal septum (mainly focussed on rectocoele) (Grossi et al. 2017), those that excise part of the rectal wall (most commonly using stapling devices) (Mercer-Jones et al. 2017), and those that suspend the rectum (mainly forms of rectopexy) (Grossi et al. 2017). The varying popularity of numerous procedures to address these problems reflects the fact that no single approach has achieved obvious clinical primacy and also that a high-quality evidence base for decision making is barely existent (Knowles et al. 2017) (Chapter 5).

Laparoscopic ventral mesh rectopexy (LVMR) was first described for external rectal prolapse in 1992 (Berman 1992), and has progressed into international practice as an effective and relatively safe, minimally-invasive approach to internal rectal prolapse (IRP) with or without rectocoele (Slawik et al. 2008, Collinson et al. 2010, Formijne Jonkers et al. 2013, Consten et al. 2015). While some large patient series provide general support for LVMR in populations of patients with a mix of symptomatic presentations

(obstructed defaecation or incontinence) due to external rectal prolapse (ERP) or IRP (Collinson et al. 2010, Formijne Jonkers et al. 2013, Consten et al. 2015, Gosselink et al. 2015, Borie et al. 2016), the utility of LVMR for patients with obstructed defaecation (and IRP only) is not well-supported by published evidence. Indeed, a recent United Kingdom's (UK) National Institute for Health Research-funded systematic review included only 18 studies in a total of 1238 patients (Chapter 5). Of these, the vast majority (16/18) of included studies provided only level IV (Oxford) evidence. While a UK-based multicentre randomised controlled trial is now recruiting (Chapter 7), this evidence base would still benefit from further observational data.

On this basis, the aims of the current study were: (1) to report longitudinal outcome data (including functional and quality of life measures) on a large series of patients from a single centre undergoing LVMR for obstructed defaecation associated with IRP (without ERP); and (2) to test the hypothesis that a small number of defined baseline or peri-operative variables can predict outcome. Data from a minority of patients in the current study have been published previously in the context of other research questions (Slawik et al. 2008, Mackenzie and Dixon 2014, Owais et al. 2014).

6.3. Methods

6.2.1. Patients

The cohort was recruited from consecutive patients aged over 18 years who underwent LVMR in North Bristol NHS Trust and Spire Hospital, Bristol (UK), between 1999 and 2016 (clinical audit approval CE35087). Study inclusion criteria required diagnosis of IRP with symptoms of obstructed defaecation and/or faecal incontinence and failure of conservative management with dietary modification, laxatives and habit training +/-

biofeedback therapy. Patients with ERP were excluded from the study. ERP were distinguished from IRP on the basis of clinical examination +/- x-ray barium defaecography (in 418 patients) and examination under anaesthesia using the circular anal dilator (CAD) device.

Prospectively collected data included patient demographics (age, gender, body mass index [BMI]), previous pelvic surgery (hysterectomy, urogenital or rectal prolapse surgery), American Society of Anesthesiologists (ASA) classification (Saklad 1941), obstructed defaecation score (ODS) (Altomare et al. 2008), Cleveland Clinic incontinence score (CCIS) (Jorge and Wexner 1993), operative information and the clinical course at specific follow-up time points. A validated quality of life (QOL) questionnaire, the Birmingham Bowel and Urinary Symptoms Questionnaire-22 (BBUSQ-22) (Hiller et al. 2002, Hiller et al. 2002), was completed pre-operatively and at regular intervals thereafter (3, 12, 18, 24, 36, 48, and 60 months), along with bowel/bladder disturbance visual analogue scores (VAS). BBUSQ-22 is composed of multi-item domains (constipation, evacuation, incontinence, and urinary). Each domain score ranges from 0 to 100, with a high score being indicative of more severe symptoms (Hiller et al. 2002). ODS and CCIS were recorded pre- and post-operatively at 3 and 12 months; the 12-month score was used in the analysis.

All patients underwent physical examination and sigmoidoscopy to diagnose concomitant solitary rectal ulcer syndrome (SRUS). Anorectal physiology (ARP) was routinely performed in patients with IRP after 2009. Before this time, it was performed only in selected patients. A radiopaque marker test was performed if patients revealed a pattern of infrequent evacuation. In addition to IRP, other pelvic floor abnormalities (e.g. rectocoele and/or enterocoele or sigmoidocoele, significant dynamic perineal

descent) were documented. Analysis was restricted to patients with at least one BBUSQ-22 assessment at 12 months or later.

6.2.2. Surgical Technique

LVMR was performed according to a standard three-port technique (Mercer-Jones et al. 2014, Coleman and Cecil 2017), starting with a peritoneal incision at the level of the sacral promontory and extending caudally (avoiding the hypogastric nerves along the side of the mesorectum) to the deepest part of the Douglas pouch, and continued to the pelvic floor. The following types of mesh were inserted during the study period (choice not being dependent on any specific clinical grounds): a) 15-cm polypropylene mesh (Prolene™, Ethicon Endo-Surgery, Cincinnati, OH, USA); b) polyester (Parietex®, Covidien PLC, Dublin, Ireland); c) biologic mesh (Permacol™ [Covidien PLC, Dublin, Ireland] or Biodesign® [Cook Medical, Bloomington, IN, USA]); d) titanium-coated lightweight polypropylene (TCLP; 20 x 4 cm; TiLOOP®, Pfm Medical, Nuremburg, Germany). The polypropylene and polyester mesh were sutured to the rectum using 3/0 braded polyethylene terephthalate (Ethibond) suture (Ethicon, Edinburgh, UK) starting at the level of the pelvic floor and continuing proximally for 15 cm; Tiloop was fixed using 3/0 polydioxanone (Ethicon, Edinburgh, UK). The tail of the mesh was then fixed to the sacral promontory using the ProTack™ fixation device (Medtronic, Boston, MA, USA), ensuring fixation into bone and avoiding the L5/S1 disc. In presence of significant posterior rectal prolapse determined by a further intra-operative CAD examination, a narrow 2-cm window was created in the mesorectal space. This dissection was extended caudally for a few centimetres and a 2/0 polyethylene terephthalate (Ethibond) suture was placed in the Cutait layer of the mesorectum and secured at the level of the sacral promontory.

A 3/0 V-Loc™ Wound Closure Device (Covidien, Mansfield, MA, USA) with a welded loop was inserted through the umbilical port into the pelvis to suture the peri-cervical fascia or (in hysterectomized women) the vaginal vault to the mesh anteriorly, followed by apposition of the uterosacral ligaments when present or simple closure of the peritoneum to bury the mesh.

6.2.3. Statistical Analysis

Data were analysed by an independent senior statistician (Dr Richard Hooper) with expertise in evaluation of complex interventions. While members of the surgical team reviewed and approved the final manuscript, they had no influence over analysis or presentation of study outcomes.

Data were analysed using Stata® V.14.0 (Stata Corporation, College Station, Texas, USA). Mean changes in ODS and CCIS from pre- to post-operative assessments were estimated from participants who had both assessments. Mean changes from baseline in BBUSQ-22 scores and bowel/bladder VAS were estimated from a mixed linear regression analysis with fixed effect of time and random effect of individual, using all non-missing outcomes (this is a valid approach if data are missing at random once observed outcomes at other times are accounted for). Baseline predictors of BBUSQ-22 at 12 months were investigated using multivariable linear regression, with results presented as mean differences with 95% confidence intervals (CI). Factors considered were age, sex, BMI, previous surgery, opioids prescribed, mesh type, Oxford radiological grading of rectal prolapse, perineal descent, SRUS, as well as baseline BBUSQ-22. For this analysis, missing BBUSQ-22 outcomes at 12 months were imputed using multiple imputation with chained equations. Missing data were imputed using the same

predictors as in the analysis model, as well as values of BBUSQ-22, bowel VAS and bladder VAS at all time-points from pre-operative to 60 months (thus incorporating ancillary information likely to improve the imputation of BBUSQ-22 at 12 months). We performed multiple imputation using 20 imputations.

Data included information on the date of the first recurrence of prolapse or symptoms (or the date of last follow-up if there was no such recurrence). Where this first event (in essence a composite outcome) was a recurrence of symptoms rather than prolapse, the time to the next prolapse was assumed to be censored (unknown) beyond this point. Predictors of prolapse-free survival were analysed using multivariable Cox regression and Kaplan-Meier survival curves, with results presented as hazard ratios (HR) with 95% CI. Data also included information separately on the date of the first mesh complication. Predictors of complication-free survival were analysed as for prolapse-free survival.

6.3. Results

Baseline characteristics are summarised in Table 6.1.

TABLE 6.1 - PATIENT CHARACTERISTICS (TOTAL N = 537).

Characteristic		
Age (median, IQR)[1]	56	(46, 65.5)
Sex, number (%)		
Males	50	(9.3%)
Females	487	(90.7%)
BMI, median (IQR)	26	(24, 28)
Previous surgery for rectal prolapse, number (%)[1]	84	(15.6%)
Previous bladder or vault surgery, number (%)[1]	155	(28.9%)
Hysterectomy (abdominal or transvaginal), number (%)[1]	61	(11.4%)
Opioids, number (%)		
None	517	(96.3%)
Tramadol only	16	(3.0%)
Strong opioids	4	(0.7%)
X-ray defaecography performed	418	(77.8%)
Oxford grade, number (%)		
II	4	(0.7%)
III	51	(9.5%)
IV	482	(89.8%)
Perineal descent, number (%)		
No	74	(13.8%)
Yes	463	(86.2%)
Mesh type, number (%)		
Polyester	202	(37.6%)
Biologic	10	(1.9%)
Polypropylene	143	(26.6%)
TCLP	182	(33.9%)
SRUS, number (%)	33	(6.1%)

[1] *One participant (two in the case of previous bladder or vault surgery) with missing data (different participants for each).*
IQR = interquartile range. TCLP = titanium-coated lightweight polypropylene. SRUS = solitary rectal ulcer syndrome.

There were 538 patients with at least one BBUSQ-22 assessment at 12 months or later, but we excluded one of these for whom mesh type was missing. In other instances, where baseline characteristics were missing they were imputed based on median values or modal categories: one patient had missing age which was imputed as the median (56 years); one had a missing record of previous surgery for rectal prolapse and was assumed to have had none; two had a missing record of previous bladder or vault surgery and were assumed to have had none; one had a missing record of hysterectomy

and was assumed to have had none. Length of follow-up varied from 1 to 12 years (median 36 months).

6.3.1. Longitudinal functional outcome data

ODS (mean reduction 16.6 points, 95%CI 16.2 to 17.1; p<0.001) and CCIS (10.3 points, 95%CI 9.5 to 11.1; p<0.001) significantly improved at 12 months post-operatively (Table 6.2).

TABLE 6.2 - CHANGE FROM PRE- TO POST-OPERATIVE ASSESSMENT OF OBSTRUCTED DEFAECATION SCORE (ODS) AND CLEVELAND CLINIC INCONTINENCE SCORE (CCIS). FIGURES SHOW MEAN, STANDARD DEVIATION (SD), NUMBER WITH NON-MISSING DATA (N), AND 95% CONFIDENCE INTERVAL (CI) AND P-VALUE FOR THE CHANGE.

	Pre-operative			Post-operative			Change			
	Mean	(SD)	n	Mean	(SD)	n	Mean	(95% CI)	n	p
ODS	20.2	(4.0)	370	3.7	(4.0)	435	16.6	16.2, 17.1	368	<0.001
CCIS	15.4	(3.0)	118	5.2	(3.4)	116	10.3	9.5, 11.1	105	<0.001

Improvements in BBUSQ-22 (mean reduction at 12 months of 23.1 points, 95% CI 22.3 to 23.8; p<0.001) and bowel VAS (mean reduction at 12 months of 78.8 points, 95% CI 74.9 to 82.7; p<0.001) were maintained at a fairly constant level with further follow-up [Figure 6.1].

	Mean	(SD)	n
BBUSQ-22			
Pre-operative	56.8	(8.1)	537
3 months	36.1	(7.1)	485
12 months	33.8	(6.2)	463
18 months	33.5	(6.2)	215
24 months	34.6	(6.7)	158
36 months	34.1	(6.3)	136
48 months	35.0	(6.4)	96
60 months	34.4	(5.8)	70
Bowel VAS			
Pre-operative	112.1	(20.4)	537
3 months	41.5	(32.9)	348
12 months	35.2	(30.2)	256
18 months	41.7	(36.2)	110
24 months	40.5	(35.2)	98
36 months	34.4	(32.7)	85
48 months	33.4	(31.5)	68
60 months	34.2	(32.3)	42
Bladder VAS			
Pre-operative	51.8	(31.6)	450
3 months	38.7	(31.7)	283
12 months	35.1	(30.1)	214
18 months	30.6	(26.5)	97
24 months	30.7	(27.1)	75
36 months	31.0	(29.3)	81
48 months	32.5	(29.6)	65
60 months	34.2	(30.6)	40

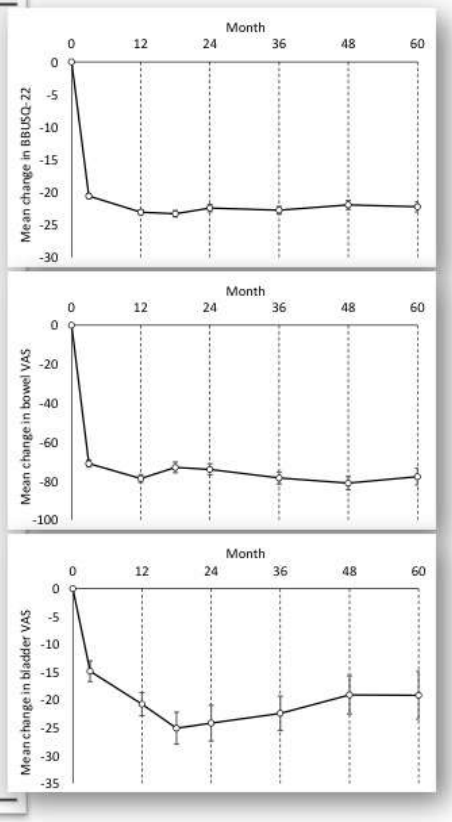

FIGURE 6.1 - BIRMINGHAM BOWEL AND URINARY SYMPTOMS QUESTIONNAIRE-22 (BBUSQ-22) (A), BOWEL (B) AND BLADDER (C) VISUAL ANALOGUE SCORES (VAS) AT DIFFERENT TIME-POINTS (MEAN, STANDARD DEVIATION [SD], NUMBER WITH NON-MISSING DATA [N] AND GRAPHS SHOWING MEAN CHANGES FROM BASELINE). ERROR BARS SHOW STANDARD ERRORS.

Improvements in bladder VAS (mean reduction at 12 months of 20.8 points, 95% CI 16.7 to 24.8; p<0.001) appeared to weaken over time, though standard errors were larger (Figure 6.1). Older age (mean difference per decade 0.55 points; 95% CI 0.12 to 0.99; p=0.013), and previous bladder or vault surgery (mean difference 2.12 points; 95% CI 0.78 to 3.47; p=0.002) were independently associated with higher BBUSQ-22 at 12 months, even after adjusting for baseline BBUSQ-22 (Table 6.3), though the effects of these variables were small compared with the improvement in BBUSQ-22 relative to pre-operative levels (Figure 6.1).

TABLE 6.3 - RESULTS FROM THE MULTIVARIABLE LINEAR REGRESSION SHOWING PREDICTORS OF BIRMINGHAM BOWEL AND URINARY SYMPTOMS QUESTIONNAIRE-22 (BBUSQ-22) AT 12 MONTHS, USING MULTIPLE IMPUTATION.

	Mean difference	(95% CI)	P-value
Age (per 10 years)	0.55	(0.12, 0.99)	0.013
Sex			0.70
Male (reference category)	0		
Female	0.38	(-1.56, 2.31)	
BMI (per scale point)	0.14	(-0.01, 0.28)	0.059
Previous surgery for rectal prolapse	0.97	(-0.59, 2.54)	0.22
Previous bladder or vault surgery	2.12	(0.78, 3.47)	0.002
Hysterectomy (abdominal or transvaginal)	1.15	(-0.68, 2.98)	0.22
Tramadol or strong opioids	-1.61	(-4.49, 1.28)	0.27
Oxford grade			0.11
II-III (reference category)	0		
IV	-1.57	(-3.50, 0.35)	
Perineal descent	1.39	(-0.32, 3.11)	0.11
Mesh type			0.060
Polyester (reference category)	0		
Biologic	-2.58	(-6.48, 1.31)	
Polypropylene	-1.85	(-3.29, -0.42)	
TCLP	-0.76	(-2.12, 0.61)	
SRUS	0.32	(-1.94, 2.58)	0.78
Pre-operative BBUSQ-22	0.09	(0.02, 0.16)	0.010

TCLP = titanium-coated lightweight polypropylene. SRUS = solitary rectal ulcer syndrome.

6.3.2. Mesh-related complications

There were 39 mesh complications in 1,640 person-years of follow-up (2.4 per 100 person years). None of the patients with a biologic mesh had a mesh complication, nor did any of the male patients. Among the 39 patients with complications, 25 had a rectal or vaginal erosion, 3 had a mesh infection, 6 had both a rectal or vaginal erosion and a mesh infection, and 5 had other mesh complications including removal of mesh due to fistula. Mesh type was strongly predictive of complication-free survival (p=0.001) on multivariable Cox regression investigating predictors of time to mesh complication

among female patients with polyester, polypropylene, and TCLP mesh (Table 6.4): patients with polypropylene mesh had the best complication-free survival (HR 0.27 relative to polyester, 95% CI 0.12 to 0.61), closely followed by patients with TCLP mesh (HR 0.32 relative to polyester, 95% CI 0.09 to 1.09).

TABLE 6.4 - RESULTS FROM THE MULTIVARIABLE COX REGRESSION SHOWING PREDICTORS OF TIME TO MESH COMPLICATION (EXCLUDING MALES, AND ALL PATIENTS RECEIVING A BIOLOGIC MESH).

	Hazard ratio	(95% CI)	P-value
Age (per 10 years)	1.01	(0.78, 1.31)	0.92
BMI (per scale point)	1.04	(0.96, 1.13)	0.35
Previous surgery for rectal prolapse	0.34	(0.08, 1.45)	0.14
Previous bladder or vault surgery	0.92	(0.41, 2.07)	0.85
Hysterectomy (abdominal or transvaginal)	1.13	(0.47, 2.74)	0.79
Tramadol or strong opioids	0.57	(0.07, 4.46)	0.60
Oxford grade			0.23
II-III (reference category)	0		
IV	0.57	(0.23, 1.42)	
Perineal descent	1.34	(0.39, 4.58)	0.64
Mesh type			0.001
Polyester (reference category)	0		
Polypropylene	0.27	(0.12, 0.61)	
TCLP	0.32	(0.09, 1.09)	
SRUS	0.30	(0.04, 2.22)	0.24

TCLP = titanium-coated lightweight polypropylene. SRUS = solitary rectal ulcer syndrome

Figure 6.2 shows Kaplan-Meier complication-free survival curves for different mesh types in female patients. No other baseline variables predicted mesh complications (Table 6.4).

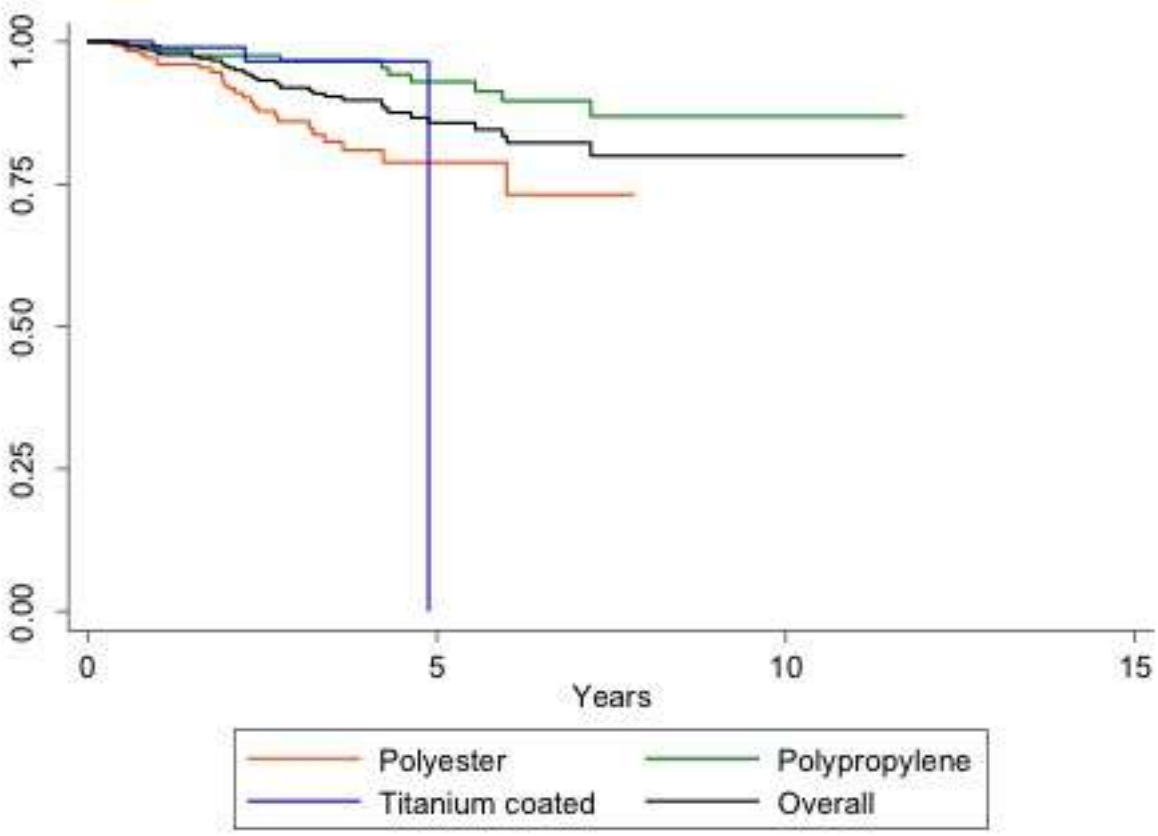

FIGURE 6.2 - MESH COMPLICATION-FREE SURVIVAL AFTER SURGERY, IN FEMALE PATIENTS (MALE PATIENTS HAD NO MESH COMPLICATIONS) BY MESH TYPE.

6.3.3. Intussusception recurrence

There were 33 recurrences of prolapse in 1,570 person-years of follow-up (2.1 per 100 person years). None of the 10 patients with a biologic mesh had a recurrence of prolapse, so the relative prolapse-free survival in this subgroup cannot be estimated. Table 6.5 shows results from a multivariable Cox regression exploring predictors of time to recurrence of prolapse among those with polyester, polypropylene, and TCLP mesh only.

TABLE 6.5 - RESULTS FROM THE MULTIVARIABLE COX REGRESSION SHOWING PREDICTORS OF TIME TO RECURRENCE OF PROLAPSE† (EXCLUDING PATIENTS RECEIVING A BIOLOGIC MESH).

	Hazard ratio	(95% CI)	P-value
Age (per 10 years)	1.13	(0.86, 1.50)	0.37
Sex			0.16
Male (reference category)	0		
Female	4.27	(0.56, 32.79)	
BMI (per scale point)	0.97	(0.88, 1.07)	0.54
Previous surgery for rectal prolapse	1.32	(0.54, 3.26)	0.54
Previous bladder or vault surgery	1.28	(0.55, 2.96)	0.56
Hysterectomy (abdominal or transvaginal)	1.10	(0.30, 4.08)	0.88
Tramadol or strong opioids	0.97	(0.28, 3.45)	0.97
Oxford grade			0.72
II-III (reference category)	0		
IV	1.22	(0.40, 3.69)	
Perineal descent	1.92	(0.56, 6.60)	0.30
Mesh type			<0.001
Polyester (reference category)	0		
Polypropylene	0.07	(0.02, 0.35)	
TCLP	2.98	(1.31, 6.75)	
SRUS	2.94	(1.05, 8.23)	0.040

TCLP = titanium-coated lightweight polypropylene. SRUS = solitary rectal ulcer syndrome. † As defined in methods (composite symptoms or anatomically proven).

Mesh type was strongly predictive of prolapse-free survival (p<0.001) [Figure 6.3]: patients receiving 15-cm polypropylene mesh had the best prolapse-free survival (HR 0.07 relative to polyester, 95% CI 0.02 to 0.35), and patients with TCLP mesh the worst (HR 2.98 relative to polyester, 95% CI 1.31 to 6.75).

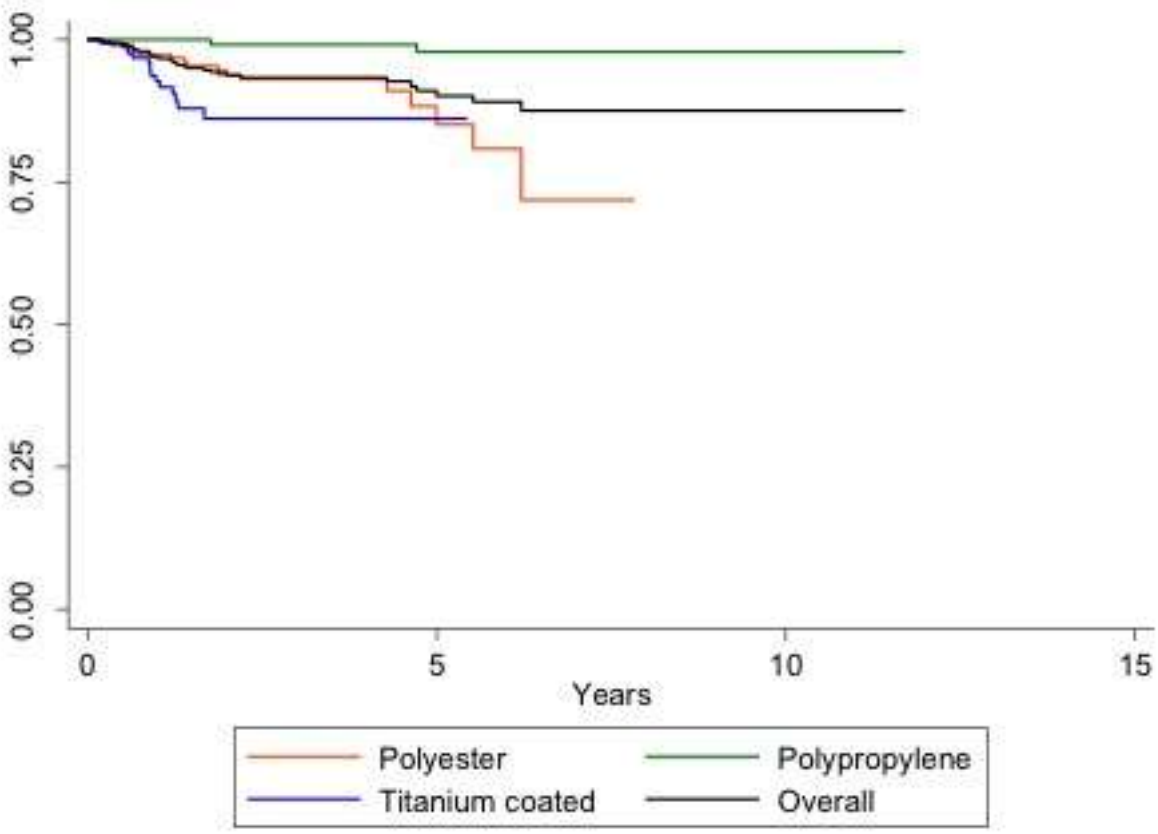

FIGURE 6.3 - PROLAPSE-FREE SURVIVAL AFTER SURGERY, BY MESH TYPE.

SRUS was independently associated with earlier recurrence of prolapse (HR 2.94, 95% CI 1.05 to 8.23, p=0.040). No other baseline variables predicted this outcome (Table 6.5).

6.4. Discussion

6.4.1. Summary of main results

This large single-centre retrospective cohort study (of prospectively collected data) assessed clinical outcomes and predictors thereof in 537 patients undergoing LVMR for IRP. The main results demonstrated significantly reduced constipation and incontinence symptoms following surgery and improvements in disease-specific QOL that were maintained to last follow-up. Older age and previous urogenital prolapse surgery were

independently associated with poorer QOL at 12 months. Mesh type significantly influenced complications and recurrence, and this is discussed in detail below.

6.4.2. Limitations

Inclusion of consecutive patients was based on pre-established criteria. Nevertheless, it is acknowledged that our study presented data only from a single surgeon and a single region of the UK, and as such, local referral practice may limit the generalizability of data.

There was evidently some attrition in the assessment of post-operative quality of life. The last recorded follow-up for any participant in the database was 30 August 2016: if this was the date at which the database ceased to be updated then there would have been 535 participants followed for at least 12 months, and 510 participants followed for at least 24 months. In contrast, BBUSQ-22 scores were only available for 467 participants at 12 months and 164 at 24 months. To mitigate possible attrition bias we used multiple imputation to impute missing outcomes at 12 months using assessments of QOL at other time-points as well as patient characteristics. Results obtained by imputation can be sensitive to the choice of imputation model, but in the present case a sensitivity analysis found that our imputation analysis and a complete case analysis produced similar results (not shown here), strengthening our confidence in the final conclusions.

Our comparison of mesh types was not randomised and as such we cannot rule out the possibility of confounding with patient characteristics, though we adjusted for effects of a number of demographic and clinical characteristics at the time of surgery. Nevertheless, we can be certain that choice of mesh did not introduce a systematic bias

i.e. this was not governed by patient baseline characteristics but rather by the mesh made available by local procurement practice at the time of surgery. The move to low molecular weight polypropylene coated in titanium was precipitated by the observation of an apparent increase in complications with the use of polyester and later confirmed statistically in the earlier published analysis by Mackenzie and Dixon (2014) The best 'performing mesh' in respect of complications and recurrence appeared to be polypropylene. Since this was the predominant mesh used in patients that were chronologically earlier in the series, it does not appear that temporal changes in mesh use were reflected in outcomes due to the learning curve.

6.4.3. Comparison with previous studies

This is not the first study of outcomes from LVMR in patients with IRP. Table 6.6 compares the current data with 11 previous studies (published 2010 to 2016), 7 of which were prospective (Collinson et al. 2010, Portier et al. 2011, Sileri et al. 2012, Franceschilli et al. 2015, Gosselink et al. 2015, Tsunoda et al. 2015, Tsunoda et al. 2016) and 4 retrospective (Formijne Jonkers et al. 2013, Gosselink et al. 2013, Borie et al. 2014, Consten et al. 2015) in design. Notable amongst these is the large retrospective cohort study of Consten et al. (2015), which reported outcomes of LVMR in a cohort of 919 patients from two centres, with a very similar follow-up to the current study (median 34 months: range 4 months to 12 years vs. median 36 months: range 12 months to 15 years). Within the cohort, 677 patients had a main diagnosis of IRP. While some data were unsegregated by baseline phenotype (there were a mix of symptomatic presentations and prolapse type: IRP vs. ERP), the investigators reported resolution of ODS symptoms in approximately 70%. Cumulative risks of mesh complication based on

Kaplan-Meier estimates (1.5% after 3, 2.9% after 5, and 4.6% after 10 years) were considerably lower than those in the current study (8.0% after 3, 14.2% after 5, and 20.0% after 10 years in female patients) and particularly so for mesh erosions or infection (at 10 years, previous study: 1.5% vs. current study 18.6% [Table 6.6]). In contrast, cumulative recurrence rates in the study by Consten et al. were slightly higher than those in the current study (recurrent IRP in 45/677: 7.5% after 3, 11.1% after 5, and 14.3% after 10 years vs. 2.1 per 100 person years: 6.6% after 3, 9.9% after 5, and 12.4% after 10 years, respectively). Other smaller studies had much lower or no mesh complication rates (Table 6.6), and variable recurrence rates from 2.5-14% (noting limitations in this method of data presentation: below).

TABLE 6.6 - STUDIES REPORTING OUTCOMES OF LAPAROSCOPIC VENTRAL MESH RECTOPEXY (LVMR) IN PATIENTS WITH INTERNAL RECTAL PROLAPSE (IRP)

Author	Year	N	Design	Median° / Mean°° follow-up, months (range)	Mesh types	Mesh Cx (%)	Mean CCCS° / ODS°°/ PAC-SYM°°°		Constipation improved (%)	FISI° / CCIS°°		QOL measures	Anatom. recurr. (%)
							pre	post		pre	post		
Collinson	2010	75	PCS	12° (3-48)	PP	0	12°	5°	86	28°	8°	NR	5.0
Portier	2011	40*	PCS	22°° (6-72)	NR	0	NR	NR	65	13.3°°	3°°	NR	2.5
Sileri	2012	34	PCS	12° (6-30)	B	0	16°	7°	NR	9°	3°	NR	5.9
Formijne Jonkers	2013	157	RCS	30°° (5-83)	PP (varied)	1.3§	NR	8.1°	66	NR	NR	NR	2.6
Gosselink	2013	151	RCS	12° (12-12)	NR	NR	2°°°	0.9°°°	NR	24°	12°	PAC-QOL, GIQLI	NR
Borie	2014	52	RCS	NR	PP	NR	16°°	7.6°°	NR	NR	NR	NR	NR
Franceschilli	2015	100	PCS	20° (6-54)	B	0	18.4°	5.4°	92	8.4°	3.3°	NR	14.0
Tsunoda	2015	26	PCS	16° (6-26)	PP	0	11°	4°	NR	30°	6°	NR	3.8
Gosselink	2015	50	PCS	12° (12-12)	PP	0	NR	NR	NR	42°	25°	GIQLI	6
Consten	2015	677	RCH	33.9° (0.4-144)	PP (varied)	4.6~	NR	NR	74	NR	NR	NR	14.2~
Tsunoda	2016	25	PCS	26° (12-42)	PP	0	11°	5°	59	30°	8°	SF-36, FIQL, PAC-QOL	4.0
Current series	2017	537	RCH	36° (12-144)	PP,PE,B,TCLP	20.0~	20.2°°	3.7°°	NR	15.4°°	5.2°°	BBUSQ-22	12.4~ †

*Cx: complications; CCCS: Cleveland Clinic constipation score; ODS: Obstructed Defaecation Syndrome score; PAC-SYM: Patient Assessment of Constipation Symptoms; FISI: Faecal Incontinence Severity Index; CCIS: Cleveland Clinic faecal incontinence score; PP: polypropylene; PE: polyester; B: biologic; TCLP: titanium-coated lightweight polypropylene; * Included 23 open and 17 LVMR; NR: not recorded. PCS: prospective case series; RCS: retrospective case series; RCH: retrospective cohort study; § Calculated on a total cohort of 233 patients including indications for LVMR other than IRP; ~ Kaplan-Meier estimate at 10 years of follow-up; PAC-QOL: Patient Assessment of Constipation Quality of Life; GIQLI: Gastrointestinal Quality of Life Index; SF-36: Short Form-36 Health Survey; FIQL: Faecal Incontinence Quality of Life scale; BBUSQ-22: Birmingham Bowel and Urinary Symptoms Questionnaire-22. † As defined in methods (composite symptoms or anatomically proven).*

Discrepancies in recurrence and complication rates between the current and previous studies merit discussion but this is necessarily limited by variability in patient selection, surgical expertise, variations in mesh, sutures, techniques, outcome definitions and particularly length of follow-up. ERP recurrence rates are known to be time dependent i.e. ranging widely from 1.6%-5.6% (D'Hoore et al. 2004, Auguste et al. 2006, D'Hoore and Penninckx 2006, Boons et al. 2010, Wijffels et al. 2011, Faucheron et al. 2012, Randall et al. 2014) within 5 years to 20% at 10 years (Foppa et al. 2014). Table 6.6 illustrates similar issues with mesh complications. The current study and that of Consten et al. (2015) have the longest follow up and the highest rates of mesh complications; that of Formijne Jonkers et al. (2013) is the only other to document any such complications and has the next longest follow up. All studies with less than 30 months' mean follow up had no documented complications. A further problem of cohort studies is that time dependency of mesh complications may lead to significant reporting bias in a population with follow up attrition (i.e. those re-presenting for long-term follow up could be presumed to do so only if problems have occurred). We and Consten et al. (2015) correctly acknowledged time-dependency of event rates by using data presentation and statistical methods that are appropriate for time series. Nevertheless, the current data, taken at face value do suggest a modest but significant rate of mesh erosion and infection after LVMR.

Our study however moves beyond Consten et al. (2015) in prediction of outcome based on baseline and perioperative variables and is facilitated in this regard by having a single centre and surgeon (reducing one source of variability). In accord with other studies (Sileri et al. 2012, Franceschilli et al. 2015), patients receiving polypropylene mesh had the best mesh complication-free survival (HR 0.27 relative to polyester), closely followed

by patients with TCLP mesh (HR 0.32). This finding is in agreement with a multicentre study on ERP suggesting that mesh erosions were more frequently associated with polyester mesh (Evans et al. 2015). It also accords with data in Table 6.6, where the current study has the highest rate of complications and is the only study to document the use of polyester (among the subgroup of female patients with polyester mesh the cumulative risks of mesh complication based on Kaplan Meier estimates were 14.0% after 3 and 21.2% after 5 years). The profound negative influence of polyester mesh is also evident from the survival curve [Figure 6.2]. An additional point is that the complication rates for biologics in the two previous studies that only used such meshes were zero (as in the small number of patients in our study who received biologic mesh). The potential benefit of biologic mesh in respect of low complication rates has led to consensus from a panel of experts that biological grafts may better suit young patients, women of reproductive age, diabetics, smokers, patients with a history of previous pelvic radiation or sepsis, inflammatory bowel disease, and intraoperative breach of the rectum or vagina (Mercer-Jones et al. 2014).

Mesh type was also strongly predictive of time to recurrence of prolapse ($p<0.001$), with polypropylene having the best recurrence-free survival, and TCLP the worst: HR 0.07 (0.02-0.35) vs. 2.98 (1.31-6.75), respectively. Rates of anatomical recurrence varied among previous studies, with lower percentages reported after LVMR using polypropylene (2.5%-5%) compared to biologic mesh (6%-14%). A recent meta-analysis attests to this point in relation to the ERP literature on LVMR (Tou et al. 2015). However, none of the 10 subjects receiving a biologic mesh in our cohort experienced a recurrence, and both a recent systematic review of data in patients with ODS (Grossi et al. 2017) and recent UK National Position Statement (ACPGBI) (Mercer-Jones et al. 2017)

considered that published evidence is currently insufficient to make a firm recommendation based on these observations. No previous study described outcomes of LVMR for IRP using either polyester or TCLP, thus comparison is not possible. Although our previous series of 48 patients with SRUS (37 of which had an IRP) showed sustained improvement in QOL and VAS after LVMR (Badrek-Amoudi et al. 2013), this pathologic finding was independently associated with earlier recurrence of prolapse in the present study (HR 2.94, 95% CI 1.05 to 8.23).

In contrast to nearly all previous studies (Table 6.6), we also explored long-term disease-specific quality of life using two validated instruments. Tsunoda et al. (2016) used validated instruments (Short-Form 36 Health Survey [SF-36], Faecal Incontinence QOL scale [FIQL], and Patient Assessment of Constipation-QOL [PAC-QOL]) to assess QOL after LVMR in 25 patients with IRP (all females) and 19 with ERP. Compared to the pre-operative assessment, almost all of the scale scores on the three QOL instruments significantly improved over time. Gosselink et al. (2013) compared the functional results of LVMR for obstructed defaecation secondary to high grade IRP in 109 patients with normal and 42 with delayed colonic transit. Although pre-operative PAC-QOL scores were higher (worse) in the latter group, the total PAC-QOL score was significantly improved in both groups at 12 months ($p<0.001$). The Gastrointestinal Quality of Life Index (GIQLI) was also improved in both groups. The same authors showed equivalent GIQLI improvements in a series of 50 incontinent patients undergoing LVMR for high grade IRP ($p=0.01$) (Gosselink et al. 2015). In the current study, we observed improvements in BBUSQ-22 ($p<0.001$) and bowel VAS ($p<0.001$) at a fairly constant level during follow-up, with older age ($p=0.013$) and previous urogenital surgery ($p=0.002$) being independent predictors of higher BBUSQ-22 at 12 months. Sustained

improvements in BBUSQ-22 and bowel VAS were analogously observed in our previous series of 50 males undergoing LVMR for IRP (Owais et al. 2014).

In previous studies (Table 6.6), LVMR showed improvement of obstructed defaecation in proportions of patients ranging from 59% to 92%, with a significant mean decrease in Cleveland Clinic constipation score (CCCS) between pre- and post-operative period of 8.4 (range, 6-13) points. We observed a 16.6 point mean reduction in ODS, which was approximately double that reported by the only other study that used this instrument (Borie et al. 2014). Improvements in faecal incontinence were also reported in most previous studies, with a mean increase of 15 points in Faecal Incontinence Severity Index (FISI). The significant reduction in CCIS observed in our cohort (10.3 points) is similar to that previously reported by Portier et al. (2011) (10.0 points), and accords with recently published international consensus (O'Connell 2016) that patients with FI and evidence of obstructed defaecation should have primary surgical correction of dynamic structural causes of defaecation disorder rather than other interventions such as sacral nerve stimulation.

6.4.4. Implications for research and clinical practice

Over the last decade, LVMR has become an increasingly popular surgical option for patients with high-grade IRP associated with either constipation or incontinence symptomatic presentations. At present, two randomised controlled trials (RCTs) are assessing the effectiveness of LVMR alone (Grossi et al. 2018) or comparing LVMR with STARR (https://clinicaltrials.gov/ct2/show/NCT01899209. Accessed July 03, 2019.) for ODS secondary to IRP. Such well-designed and adequately powered RCTs may provide more reliable long-term outcomes, particularly for QOL but will not be able to address

the incidence or risk factors for mesh complication or prolapse recurrence by nature of design (low prevalence of complication and long-term follow up required). The current study adds significantly to the existing literature of observational data by reinforcing the following views: (1) after LVMR, efficacy is maintained in terms of symptoms and improvements in QOL in the medium term; (2) overall recurrence rates are low and well below those reported in previous pooled analyses of other techniques. It does however highlight the risk of mesh-related complications, providing some indication of risk factors for both recurrence and mesh complication. Such data are important since they may provide specific hypotheses for evaluation in future prospective cohort studies and / or may be modifiable in clinical practice (for instance in choice of whether mesh is used, or which mesh is used). This point is timely given the significant current international backlash against the use of transvaginal mesh manifest as high media visibility (http://www.bbc.com/news/health-39567240 Accessed July 03, 2019) and multiple high-quantum class litigations (https://www.classaction.org/transvaginal-mesh-lawsuit. Accessed June 26, 2019.). The clear differences in risk between transabdominal and transvaginal mesh are well-acknowledged by specialists and learned bodies, some of which have provided recent position statements to this effect (Mercer-Jones et al. 2017). Nevertheless, patients are rightfully concerned to know, and should be informed of, risks of failure and complications based on available data.

Chapter 7 - Stepped-wedge randomised trial of laparoscopic ventral mesh rectopexy in adults with chronic constipation: study protocol for a randomized controlled trial.

7.1. Background

The current trial forms part of an NIHR-funded programme (PGfAR: RP-PG-0612-20001). An overview of the CapaCiTY programme is provided as a scheme and includes a series of interlinked studies that answer the important questions for patient care (Figure 7.1).

A rolling program of national recruitment will provide a large cohort of well-defined patients for 3 subsequent studies over 5 years. The focus will be on generating real life evidence from pragmatic studies which will provide valid clinical outcome measures, and address patient acceptability and cost. Armed with such data it will be possible to develop an NHS management algorithm for CC which will meet patient, clinician and policy aims.

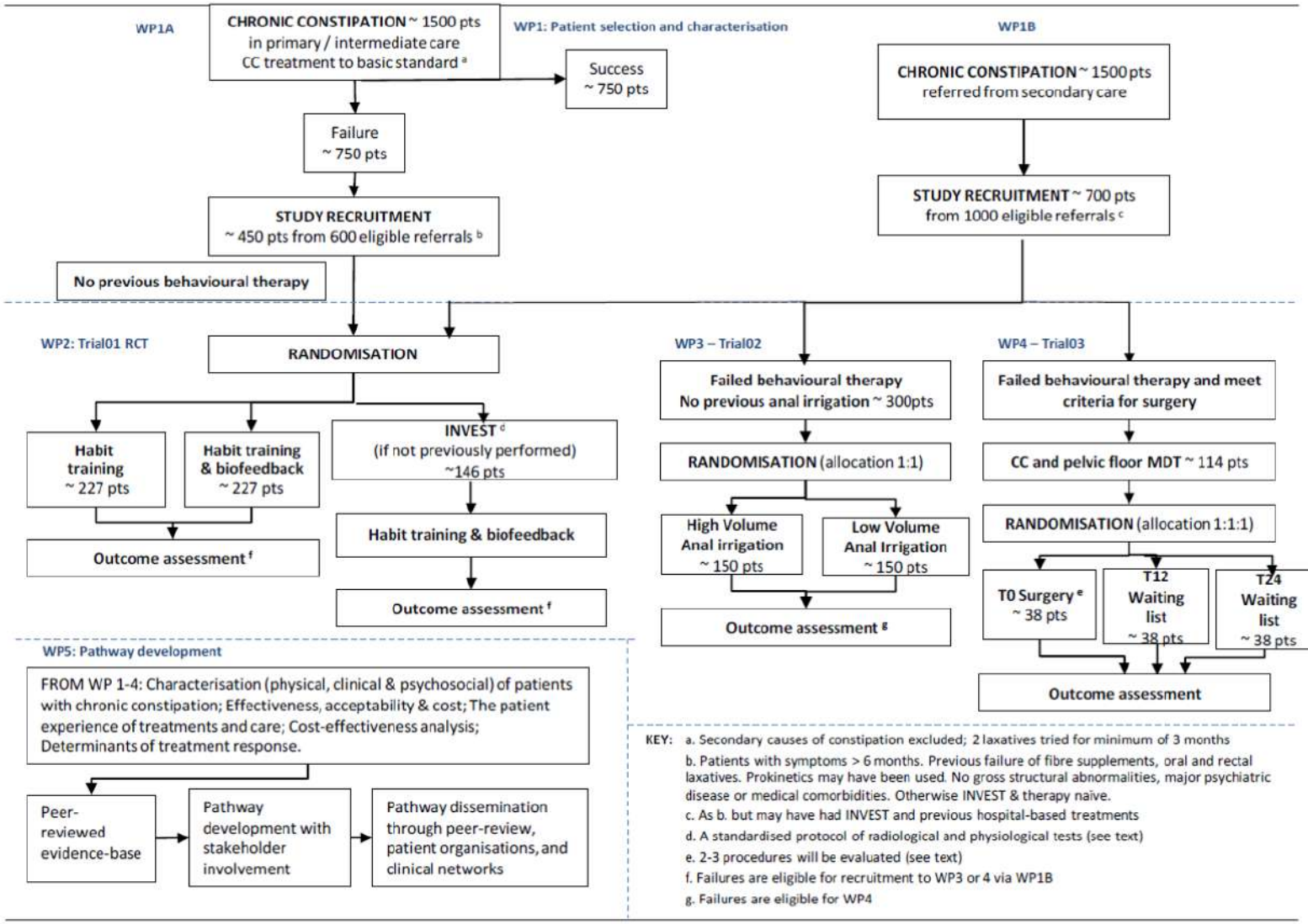

FIGURE 7.1 - CAPACITY PROGRAMME - DESIGN OVERVIEW WITH APPROXIMATE NUMBERS AT EACH STAGE.

7.1.1. Specific clinical background to the trial of laparoscopic ventral mesh rectopexy (LVMR)

In most UK practices, patients are first referred to specialist nurses for a variety of nurse-led behavioural interventions to improve defaecatory function. A range of cohort studies,(Chiotakakou-Faliakou et al. 1998) RCTs,(Bleijenberg and Kuijpers 1994, Koutsomanis et al. 1995, Glia et al. 1997, Heymen et al. 1999, Chiarioni et al. 2006, Heymen et al. 2007) reviews,(Rao 2011) guidelines,(Bharucha et al. 2013) meta-analysis(Enck et al. 2009) and a Cochrane review(Woodward et al. 2014) attest to the general success of this approach. Specific methodological issues are being addressed by CapaCiTY study 1 (Figure 7.1).

Patients failing behavioural interventions may progress to anal irrigation (CapaCiTY study 2). However, despite these approaches, some patients will have persistent intractable symptoms. When non-surgical therapies fail, a decision must be made whether to offer surgical intervention. Decision-making is greatly influenced by local expertise, commissioning and personal enthusiasm for particular interventions,(Knowles et al. 1999, Knowles et al. 2009, Lindsey and Knowles 2011) balanced against poor results in some patients.(Knowles et al. 2009) Currently, there is thus large and difficult-to-justify variation in surgical practice according to need and type of procedure. The need to reduce variations in practice, based on available evidence, has been a perpetual theme of recent national specialty group discussions(6th Annual National Pelvic Floor Meeting (National Pelvic Floor Society). October 2012. Newcastle) with various initiatives proposed. A Multidisciplinary Decision Team (MDT), incorporating expertise from nurses, gastroenterologists, urogynaecologists, colorectal

surgeons and psychologists to promote appreciation of the whole pelvic floor (bladder, vagina, uterus and bowel), could reduce the potential for inadequately-informed and potentially harmful interventions in poor surgical candidates,(Knowles et al. 2009) but the utility of this approach has not been formally tested. Further, there are few data on outcomes in well-characterised patient cohorts or rational criteria for patient selection. In practice, there are few pelvic floor procedures which are commonly employed for patients with CC, these being forms of rectopexy and rectocoele repair in conjunction with urogynaecological approaches to other organ prolapse.(Maher et al. 2010) Other procedures are only occasionally performed in highly selected patients (e.g. colectomy/ileostomy)(Knowles et al. 1999), or should only be performed on a research protocol basis (e.g. stapled transanal resection)(Bharucha et al. 2013) or are subject to specialist commissioning approval (e.g. sacral nerve stimulation)(Kamm et al. 2010, Knowles et al. 2012). Laparoscopic ventral mesh rectopexy (LVMR) is established as a treatment for external full thickness rectal prolapse(D'Hoore et al. 2004, Boons et al. 2010, Wijffels et al. 2011) but is now being widely performed internationally (including many centres in the UK) on large numbers of patients with defaecatory problems concomitant with evidence of pelvic floor weakness - mainly rectocoele and intussusception.(Slawik et al. 2008, Collinson et al. 2010, Portier et al. 2011, Wong et al. 2011, Badrek-Amoudi et al. 2013, Formijne Jonkers et al. 2013, Gosselink et al. 2013, Owais et al. 2014) The evidence needs for LVMR relate to the following observations:

a) Patient selection:

- rectocoele and intussusception are present in at least 40% of asymptomatic females, detection depends significantly on method of assessment,(Shorvon et al. 1989, Palit et al. 2014) and they frequently co-exist;(Thompson et al. 2002)
- the evident structural abnormality often belies a complex multifactorial problem with several contributing aetiologies that cannot be addressed by surgery alone;(Pescatori et al. 2007)
- structural correction (by a variety of approaches) often poorly correlates with functional outcomes.(Christiansen et al. 1995, Roman and Michot 2005, Vermeulen et al. 2005)

b) Lack of trial evidence of efficacy:

- evidence is based solely on short-term observational data obtained in the most part from individual expert case series(Collinson et al. 2010, Wahed et al. 2012, Evans et al. 2014, Mackenzie and Dixon 2014) and to some extent by evolving patient registries (populated by the same experts);
- outcomes have generally been based on poorly validated measures (e.g. patient global rating scales)(van den Esschert et al. 2008) and some bespoke summative scores (e.g. obstructive defaecation score [ODS] [46, 65])(Badrek-Amoudi et al. 2013, Borie et al. 2014), which were originally developed to show the benefit of surgery;(Jayne et al. 2009, Hasan 2012)
- there is concern that objectively-determined long-term outcomes of LVMR using validated measures will not match those from enthusiastically driven case series (as observed for numerous other surgical procedures with the intent of addressing CC).(Knowles et al. 2009)

c) Risk:

- while early data show that LVMR is relatively safe from immediate complications, it is acknowledged that the placement of a mesh in the pelvis is a high risk strategy due to problems of migration, infection and erosion.(Abbott et al. 2014) The use of mesh placed trans-vaginally has now led to class actions in all states of the USA amounting to billions of dollars of law-suits (http://www.drugwatch.com/transvaginal-mesh/lawsuit.php). Several countries (including Scotland) (http://www.bbc.co.uk/news/uk-scotland-scotland-politics-27884794) have suspended its use on this basis. While placement of mesh trans-abdominally is recognised to be safer (no exposure to vaginal bacterial flora), and biological meshes may reduce this complication (compared to synthetic),(Jia et al. 2008, Min et al. 2013, Smart et al. 2013) there are still reported morbidity rates in the 1-2% range;(Johnson et al. 2003, Smart et al. 2013, van Geluwe et al. 2013)
- as with all other pelvic floor operations, some patients may be made functionally worse by surgery due to worsening of evacuation problems, new problems of incontinence caused by altered pelvic floor dynamics(Zbar et al. 2003) and chronic pelvic pain or dyspareunia.(Smart et al. 2013) Such problems are then very difficult to correct by any method.

Such is the debate regarding LVMR that almost all international coloproctology meetings have whole sessions dedicated to its discussion (especially the issue of mesh complications); a recent consensus report has also been published.(Zbar et al. 2003) It is clear that while these complications may be limited by good technique and perhaps choice of mesh, they will not be eradicated. Thus, it can be argued that the future of

LVMR depends not on the very small observed differences in long-term mesh complications (e.g. 1.0-2.0% of patients) but on a fundamental evaluation of whether the procedure is actually clinically beneficial, i.e. whether these complication rates would be deemed acceptable (provided patients are consented to the risk) if the patients benefit was sufficiently large. The aim of the CapaCiTY study 3 is to address this knowledge gap.

7.1.2. Specific study rationale

The overall rationale is to address the main objectives (see below) within a controlled trial. We have used a stepped-wedge randomised trial design which permits observer-masked data comparisons between patients awaiting intervention with those who have undergone surgery. Contrary to most stepped-wedge trials individual patients are randomised rather than clusters. In brief (more detail below), eligible participants based on clinical evaluation and radiophysiological investigations (INVEST) will be randomized to three arms with different delays before surgery (Figure 7.2).

In all arms there will be a period of 4 weeks post-eligibility to arrange the logistics of surgery (T–4 weeks to T0) and ensure that patients have returned to their normal life routine after various assessments. LVMR will be performed at T0 in group I; T12 (12 weeks) in group II; T24 (24 weeks) in group III. Unavoidably, participants will be aware when surgery is undertaken: this however fortuitously meets the assumptions of the stepped-wedge design, i.e. no effect of treatment is expected until surgery has been performed. Efficacy outcome data will be collected at equally stepped time points (T0, 12, 24, 36, 48 weeks).

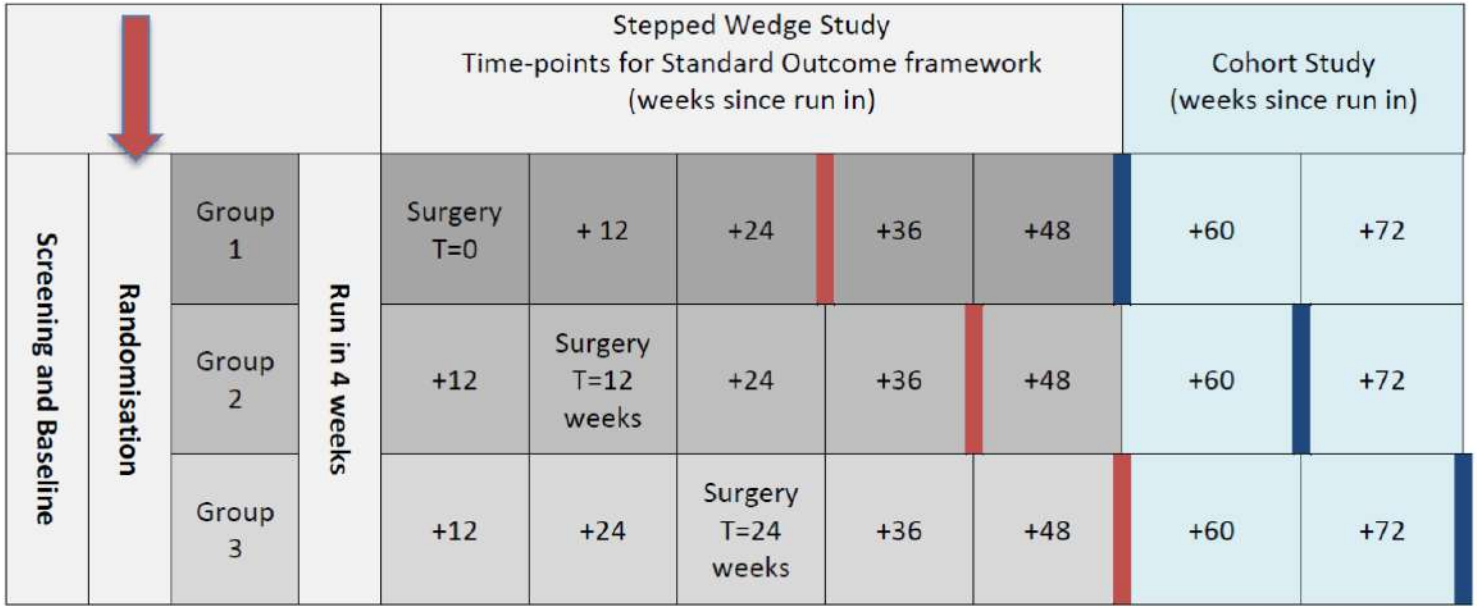

FIGURE 7.2 - CAPACITY STUDY 3 SCHEME DIAGRAM

This is, in effect, a modification of a standard parallel arm wait list control design, but with several advantages. First, a stepped-wedge design is more efficient and thus improves recruitment feasibility (the bane of nearly all surgical trials). Despite the multicentre approach of this study, the problems of recruitment cannot be under-estimated. Simulation demonstrates that a parallel arm design requires a much larger sample size than that proposed for the current study at the same power. Secondly, the trial design means that there is only a 1 in 3 chance (rather than one in 2 for a parallel arm) of waiting 6 months for surgery, which is more acceptable to patients.

7.1.3. Risks and benefits of participation

The risks of trial participation are considered very low over and above standard surgical risks. The intervention proposed is already offered to patients in specialist centres throughout the UK and internationally. The only difference conferred by participation is that the intervention will be randomly allocated by time and very carefully assessed. CC is a chronic condition (especially by the time conservative treatments have failed) and thus allocation to waiting times of up to 24 weeks poses no clinical risk. Radio-physiological tests (INVEST) are required to select patients with appropriate structural pelvic floor problems for surgery. These would be performed in routine clinical practice for all patients undergoing LVMR and will also be mandated for the trial using specified techniques and equipment. While this may lead to slight variance from normal practice, the fundamental tests and their safety remain unchanged. Such tests have been performed daily in most specialist centres for up to 30 years without any recorded complication (Barts

Health experience is over 10,000 patients). A small ionising radiation dose is required for two tests (covered below). A number of questionnaires contain personal questions about bowel problems and the effect of these on QOL and psycho-behavioural functioning, however all have been used in studies of similar patients previously. The design of the study requires data collection at time-points additional to those required for the analysis of the primary and secondary endpoints. However, this streamlines the logistics and management of the study participants through the course of the study whilst ensuring blinding is maintained and eliminating observer bias. This small additional burden on participants has been carefully balanced against the obvious benefits of the design and efficiencies of sample size gained, reducing overall number of participants required to undergo surgery.

The benefits of participation are that patients will receive a very high standard of surgery (the most experienced UK surgeons will be participating). Further, by design, the fidelity of surgical technique will be standardised and tightly scrutinised (including by preceptor- and mentorship if required); they will also receive a high standard of monitored care as a consequence of the detailed protocol.

7.2. Design and methods

Stepped-wedge randomised trial of LVMR in adults with chronic constipation (n=114), which follows the 'Standard Protocol Items: Recommendations for Interventional Trials' (SPIRIT) guidelines (see Additional file 9). Randomized to three equal arms (n = 38) with different delays before surgery. LVMR will be performed at T0 in group I; T12 (12 weeks) in group II; T24 (24 weeks) in group III.

7.2.1. Trial objectives and Endpoints

7.2.1.1. Primary objective

To determine the clinical efficacy of LVMR compared to controls at short-term follow up (24 weeks).

7.2.1.2. Secondary objectives

1. To determine the clinical effectiveness of LVMR in the medium-term (to 48 weeks to a maximum of 72 weeks).
2. To determine pre-operative determinants of outcome.
3. To determine relevant health economics for LVMR.
4. To qualitatively evaluate patient and health professional experience of LVMR.
5. Assessment of 30-day morbidity and mortality rates.

7.2.2. Trial Outcomes

7.2.2.1. Primary outcome

Primary clinical efficacy endpoint based on PAC-QOL: total score (as continuous variable) at 24 weeks post-surgery compared to pre-surgery controls.

Secondary clinical efficacy endpoints based on PAC-SYM score: total score (as continuous variable) at 24 weeks post-surgery compared to pre-surgery controls.

7.2.2.2. Secondary Outcomes

All outcomes within the standardised outcome framework will be analysed to compare baseline values with 24- and 48-weeks post-surgery follow up. When further follow up is obtained (time permitting), these data will also be reported at later time points, 60 and 72 weeks.

- Response to treatment defined as a 1-point (or greater) reduction in PAC-QOL score (Marquis et al. 2005, Dubois et al. 2010);
- PAC-QOL: individual domains and total score (as continuous variables);
- PAC-SYM score: individual domains and total score (as continuous variables);
- A two week patient diary (for 2 weeks prior to each assessment) to record bowel frequency and whether each evacuation was 'spontaneous (no use of laxatives) and / or complete'; a journal will also capture concurrent medication, health contacts, time away from normal activities (including work) since the patient's last visit;
- Generic QOL: EQ-5D-5L descriptive system and EQ-VAS (Curtis and Netten 2006). Note: EQ-VAS has a SD of approximately 30 points: a 10% difference in VAS deemed clinically significant can be detected with the large sample sizes proposed;
- Patient Health Questionnaire-9 (PHQ-9) (Roman and Michot 2005, Vermeulen et al. 2005);
- Generalized anxiety disorder questionnaire (GAD7) (Evans et al. 2014);

- Global patient satisfaction / improvement score (VAS) and whether they would recommend LVMR to other patients;
- Potentially modifiable cognitive and behavioural psychological variables shown to predict onset and perpetuation of other functional bowel symptoms: negative perfectionism (van Geluwe et al. 2013), avoidant and 'all or nothing' behaviour subscales of the chronic constipation-behavioural response to illness questionnaire (CC-BRQ) (Evans et al. 1992), and brief illness perception questionnaire-chronic constipation (BIPQ-CC) (Broadbent et al. 2006);
- St Marks Incontinence score (for concurrent symptoms) (Vaizey et al. 1999);
- Baseline brief sexual function questionnaire (Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire-12 [PISQ-12] for women (Rogers et al. 2001) and Male Sexual Health Questionnaire-Ejaculatory Dysfunction [MSHQ-EjD] Short Form for men (Rosen et al. 2004)).

7.2.2.3. Specific adverse events and surgery-specific data

- Perioperative findings, e.g. scarring, adhesions, tissue laxity, pelvic depth, ovarian or uterine pathology;
- procedural data: duration of surgery, blood loss, approach (laparoscopic vs. conversion to open), type of mesh and sutures (make, diameter, number);
- length of post-operative stay;
- 30-day re-admission;
- complications: 30-day morbidity and mortality;
- specific outcomes, e.g. dyspareunia and sexual function, pelvic pain, urinary dysfunction, new onset of faecal incontinence, early mesh complications (displacement, erosion, infection);

- early clinical recurrence of structural defect e.g. prolapse or rectocoele based on rectal examination with/without adjunctive investigations (as clinically indicated).

7.2.3. Study setting

Specialist centres across UK with surgical expertise in LVMR, approximately 10 NHS Trusts will recruit to the study. Surgeon's eligibility is based on minimum of 50 LVMR previously performed and independent assessment of adherence to defined LVMR procedural sequences.

7.2.4. Recruitment

Patients attending colorectal surgical services for constipation will be eligible for recruitment and assessed against the eligibility criteria. Such patients will mainly include referrals from secondary care. These will be identified and invited for eligibility assessment by outpatient teams. Some patients may have progressed through earlier CapaCiTY01 and/or CapaCiTY02.

7.2.4.1. Inclusion Criteria

- Age 18-70 years.
- Patient self-reports problematic constipation.
- Symptom onset greater than 6 months prior to recruitment.
- Symptoms meet American College of Gastroenterology definition of constipation (American College of Gastroenterology Chronic Constipation Task 2005).
- Constipation failed treatment to a minimum basic standard (NHS Map of Medicine 2012(http://mapofmedicine.com/access-map/) (lifestyle and dietary measures and ≥2 laxatives or prokinetics) tried (no time requirement) (Figure 7.3).

- Ability to understand written and spoken English (due to questionnaire validity).
- Ability and willingness to give informed consent.
- Failure of non-surgical interventions (minimum of nurse-led behavioural therapy).
- Internal rectal prolapse as determined by clinical examination and INVEST, fulfilling the two following diagnostic criteria:
    - intra-anal or intra-rectal intussusception with/without other dynamic pelvic floor abnormalities (e.g. rectocoele, enterocoele, perineal descent);
    - deemed to be obstructing on defaecography, i.e. trapping contrast and/or associated with protracted or incomplete contrast evacuation using normal ranges (Palit et al. 2014) (by expert review).

7.2.4.2. Exclusion Criteria

The study interventions necessitate the exclusion of major causes of secondary constipation. In detail:

- Significant organic colonic disease (red flag symptoms, e.g. rectal bleeding prior investigated); inflammatory bowel diseases; megacolon or megarectum (if diagnosed beforehand [the study will provide a useful estimate of the prevalence of such cases in referral practice]); severe diverticulosis/stricture/birth defects deemed to contribute to symptoms (incidental diverticulosis if known not an exclusion).
- Major colorectal resectional surgery.

- Current overt pelvic organ prolapse (bladder, uterus) or disease requiring obvious surgical intervention other than LVMR.
- Previous rectopexy.
- Sacral nerve stimulation (SNS) *in situ*.
- Rectal impaction (as defined by digital and abdominal examination: these form part of the NHS Map of Medicine basic standard) (http://mapofmedicine.com/access-map/).

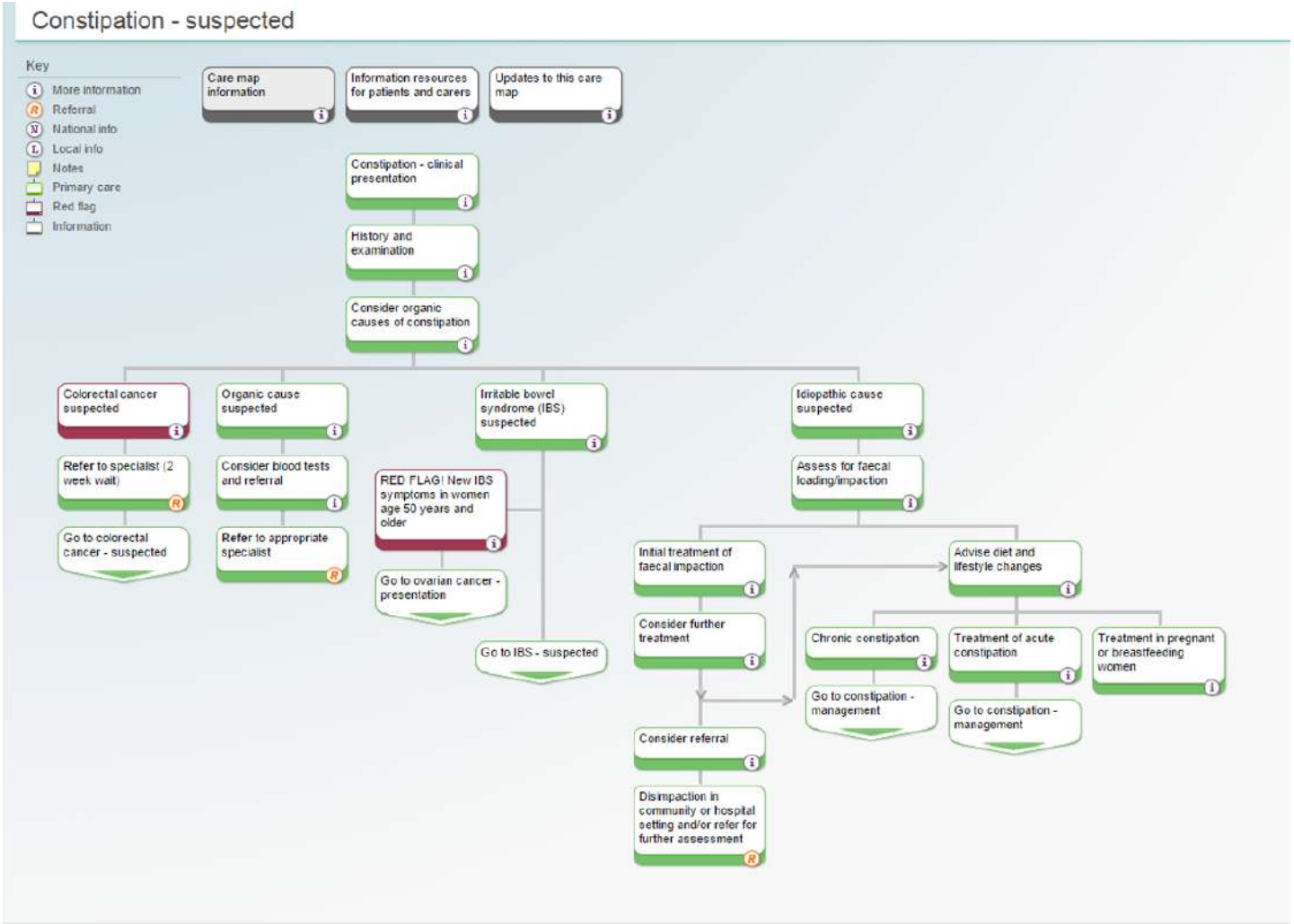

FIGURE 7.3 - NHS MAP OF MEDICINES – CONSTIPATION.

- Significant neurological disease deemed to be causative, e.g. Parkinson's, spinal injury, multiple sclerosis, diabetic neuropathy (not uncomplicated diabetes alone).
- Significant connective tissue disease, e.g. scleroderma, systemic sclerosis and systemic lupus erythematosus (not hypermobility alone).
- Significant medical comorbidities and activity of daily living impairment (based on Barthel index ≤11 in apparently frail patients).
- Major active psychiatric diagnosis, e.g. schizophrenia, major depressive illness and mania.
- Chronic regular opioid use (at least once daily use), where this is deemed to be the cause of constipation based on temporal association of symptoms with onset of therapy.
- Pregnancy or intention to become pregnant during study period.
- Known severe intra-abdominal adhesions.

7.2.5. Study Procedures

7.2.5.1. INVEST- Radio-physiological investigations

Participants will have undergone standard (clinically routine) investigations to determine eligibility for surgery. However, some patients may have missed specific tests that are required to meet the INVEST standard of the overall programme (or not had tests conducted in last 12 months). In such cases, individual missing investigations will be performed to meet the standard below, with the exception of whole gut transit studies. In order to avoid unnecessary repeated radiation, whole gut transit studies performed in the last 12 months (even if using a different marker protocol) may be

carried forward if a clear diagnosis of either delayed or normal whole gut transit time has been confirmed.

Routine NHS practice (10-day NHS rule) will apply in respect of women between menarche and menopause. Participants who may potentially be pregnant will have a serum or urine pregnancy test performed as per routine care.

INVEST includes:

a) Anorectal manometry using high-resolution methods(Mahieu et al. 1984, Womack et al. 1985, Roberts et al. 1992) to determine defined abnormalities of rectoanal pressure gradient during simulated evacuation. (Rao et al. 2004, Bharucha et al. 2013, Ratuapli et al. 2013)

b) Balloon sensory testing using standardised methods(Farthing and Lennard-jones 1978, Jameson et al. 1994) (2 ml air per second to maximum 360 ml) to determine volume inflated to first constant sensation, defaecatory desire and maximum tolerated volumes. Rectal hyposensation and hypersensation defined in accord to gender-specific normative data on 91 healthy adults.(Zarate et al. 2008) The rectoanal inhibitory reflex will also be elicited by 50 ml rapid inflation (if necessary in 50 ml aliquots up to 150 ml).

c) Fixed volume (50 ml) water-filled rectal balloon expulsion test(Barnes and Lennard-Jones 1985, Preston and Lennard-Jones 1985, Rao et al. 2004, Bharucha et al. 2013) in the seated position on a commode. Abnormal expulsion is defined as abnormal if failure to expel within 1.0-minute effort for men and 1.5 minutes for women. (Oncu et al. 2010)

d) Whole gut transit study using serial (different shaped) radio-opaque markers over 3 days with single plain radiograph at 120 hours. (Hinton and Lennard-Jones 1968, Evans et al. 1992)

e) Fluoroscopic evacuation defaecography using rectal installation of barium porridge to defaecatory desire threshold (or maximum 300 ml) and evacuation on a radiolucent commode (Mahieu et al. 1984, Mahieu et al. 1984, Womack et al. 1985, Roberts et al. 1992, Palit et al. 2014) with pre-opacification of the small bowel (for enterocoele). Radiation dose, proportion of contrast evacuated, and time taken will be recorded, as well as 'functional' (i.e. pelvic floor dyssynergia) and 'structural' features deemed obstructive to defaecation (e.g. rectocoele, enterocoele and intussusception). (Zarate et al. 2008, Bharucha et al. 2013)

Participants will be given the results of investigations by the physiologist or radiologist.

7.2.5.2. Laboratory assessments

Serum or urine pregnancy testing will be performed by local NHS biochemistry laboratories as per standard NHS policy prior to radiological and surgical procedures.

7.2.5.3. Pelvic floor MDT confirmation

As part of the whole CapaCiTY programme, a national MDT has been convened to develop a standard set of criteria for surgical eligibility to be used by local MDTs. These criteria have been coalesced into a trial CRF that will be used to validate eligibility for each patient before randomisation.

7.2.5.4. Randomisation procedures

Randomisation will be delivered following recruitment (after full eligibility and all baseline assessments). Randomisation will be stratified by sex and females further stratified by centre. The Pragmatic Clinical Trials Unit has developed a validated online randomisation system which will be accessed by suitably trained and delegated researchers at recruiting sites and will follow the PCTU approved standard operating procedure for the study.

7.2.5.5. Blinding

Patients and clinicians are necessarily aware of allocation to different waiting times. For quantitative analysis, an analysis plan will be developed and signed off by investigators and statisticians who are blind to allocation status and index intervention. No quantitative analysis will be undertaken until the analysis plan is signed off.

7.2.6. Study interventions

7.2.6.1. Laparoscopic ventral mesh rectopexy (LVMR) (Figure 7.4)

Participants will attend for surgery at their allocated time with admissions procedures as per routine clinical care with normal preparation, e.g. bowel cleansing.

Perioperative care will proceed with normal adjuncts (informed NHS consent, WHO surgical checklist, appropriate broad-spectrum antibiotic prophylaxis, venous thromboembolism [VTE] prevention, patient warming and urinary catheter insertion). Surgery can be performed as a day case procedure within an enhanced recovery programme,(Powar et al. 2013) although most patients will have an overnight stay. Consent will include discussion of the risks of conversion to open surgery and specific

complications listed below. A phosphate enema or similar (optional) may be used to clear the rectum.

Exact surgical technique will be surgeon-specific (based on individual preference) but in accord with expert guidance (Mercer-Jones et al. 2014) and training. All participating surgeons will require sign-off by a delegated surgical team provided by the Pelvic Floor Section of the Association of Coloproctology.

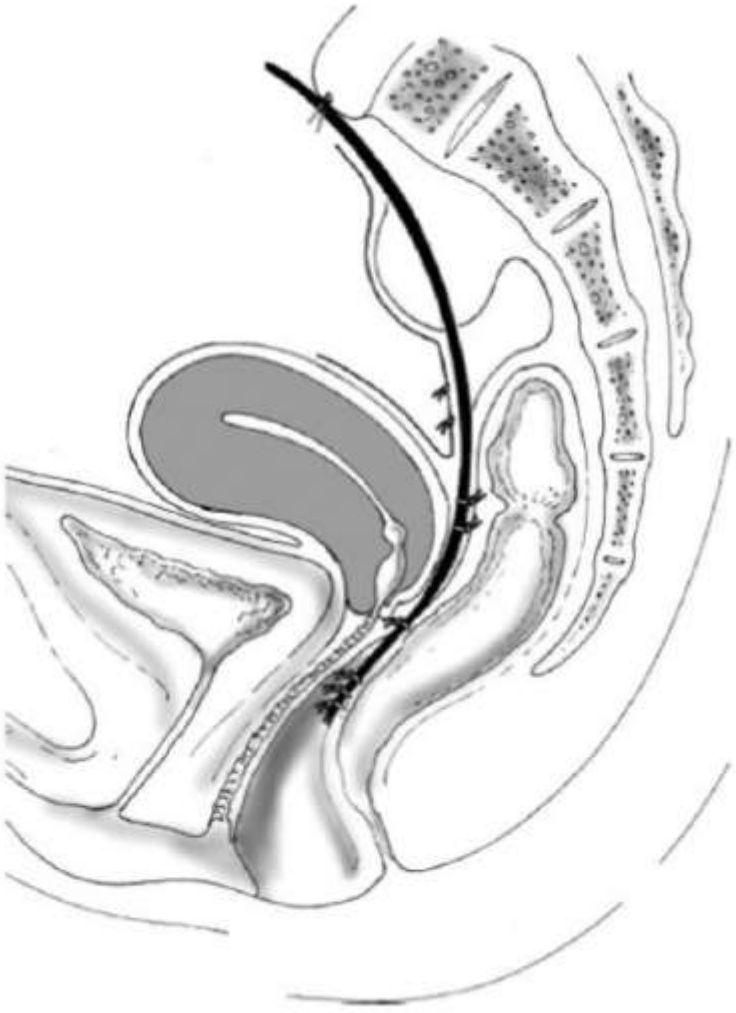

FIGURE 7.4 - SCHEMATIC DIAGRAM OF LAPAROSCOPIC VENTRAL MESH RECTOPEXY (LVMR).

Where required, preceptorship will be provided to meet sign off requirements (at the time of writing, all participating surgeons are experts in this technique).

In brief, after positioning the patient (modified lithotomy position on nonslip mat) and port-site insertion (using standard equipment and technique), the rectosigmoid junction is retracted to the left and a peritoneal incision is made over the right side of the sacral promontory and extended in an inverted J-form along the rectum and over the deepest part of the pouch of Douglas. Special care is taken not to damage the right hypogastric nerve. Denonvillier's fascia is incised and the rectovaginal septum is broadly opened. Limited rectal mobilization and lateral dissection is performed as required to expose the distal rectum and pelvic floor. A strip of trimmed mesh (biologic or synthetic) is inserted. Using non-or slowly absorbable sutures (PDS recommended), the mesh is sutured to the ventral aspect of the distal rectum and further fixed to the lateral seromuscular borders of the rectum proximal and distal to the incised pouch of Douglas +/- pelvic floor. The mesh is fixed upon the sacral promontory using either sutures or an endofascia stapler. Limited traction is exerted on the rectum as required to obliterate the intussusception +/- rectocoele. If deemed necessary, the posterior vaginal fornix may be elevated and sutured to the anterior aspect of the mesh; this allows closure of the rectovaginal septum and correction of a mid-compartment prolapse, if present. The lateral borders of the incised peritoneum are then closed over the mesh. This elevates the new pouch of Douglas over the colpopexy and completely covers the mesh with peritoneum. No drain is usually required. Ports should be closed directly (endoclose for lateral ports) owing to the high risk of early and late port site hernias in this group of patients with potential connective tissue laxity.

Post-operative management will be as per routine clinical care. This is usually an overnight hospital stay followed by urinary catheter removal, mobilisation and discharge. Post-operative laxatives use is standardised to a weaning course of

Movicol/Laxido TDS immediately post-operatively for 1 day, then reduced according to ease of bowel movements. Medication will be recorded on drug chart by anaesthetists post-operatively. This prevents post-operative constipation from immobility, narcotics and general anaesthesia, which if left untreated may cause painful straining on the mesh and thus protracts in the sacral promontory periosteum, potentially leading to readmission. Surgeon should aim to discharge patients 1 day post-operatively. Length of stay will however be determined by clinical evaluation and may be longer if required.

Quality control of LVMR procedures will be conducted according to expert panel review, as per relative standard operative procedure (SOP).

7.2.6.2. LVMR 30-day follow up

Clinical recurrence of rectal prolapse will be determined based on physical examination. Morbidity and mortality data will be collected, in addition to treatment of any complications arising from LVMR surgery. 30-day re-admission rates will also be recorded. A CRF will be used to capture intra- and post-operative data (see surgery-specific outcomes).

7.2.6.3. Concomitant medications

It is inevitable that participants will seek recourse to laxatives and other dietary supplements during the course of the programme. Experience shows that complete prohibition can lead to unreported laxative use, which might confound findings. Although we will strongly discourage *ad libitum* medication usage and specify a defined breakthrough regimen, we will record co-treatment with sufficient fidelity and integrity to enable use as covariates in analyses using a specific diary for this purpose. A

concomitant medications list including a shortlist of contributory or confounding medications will be used to filter on data entry.

7.2.7. Schedule of assessment (Figure 7.5)

7.2.7.1. Visit 0 - Pre-Screening: Eligibility assessment

A suitably trained and delegated local researcher will screen for basic eligibility within outpatient clinics or by phone (or later face-to-face interview based on patient choice) on the basis of a simplified inclusion / exclusion criteria proforma and listed for LVMR (in some cases/NHS settings based on preliminary MDT review). Participants will be recorded on a screening log and each will be allocated a sequential study number. Eligible participants will be provided with adequate explanation of the aims, methods, anticipated benefits and risks of the study and will take away or be posted an invitation letter and patient information sheet. Patients will be given at least 24 hours to consider participation.

The study screening number will be allocated as follows:

- Study Code 03;
- Site Code – 3 letter code for each site;
- Participant Code – 4 digit code given consecutively and attributed at each site.

For example, the first participant screened at Bart's Health Trust would be assigned the code 03-BLT-0001. If they were then recruited to the study, they retain this number.

			Stepped Wedge					Cohort	
Assessment	**V0** Pre-Screening	**V1*** Screening & Baseline	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**
Timeframe between visits	-1 day	-4 weeks	T0	+ 12 weeks	+ 12 weeks	+12 weeks	+12 weeks	**+12 weeks**	**+12 weeks**
MDT review (preliminary[1] and final[2])	X[1]	X[2]							
Brief screening and providing patient information	x								
Informed Consent		x							
Structured history including eligibility assessment, demographics, medical history, medications, clinical examinations incl. POPQ		x							
Urine and Serum Pregnancy Test where applicable		x	**Grp 1**	**Grp 2**	**Grp3**				
Baseline assessments (Rome IIIQ –ConstipationQ & IBSQ, Cleveland Clinic Q, pain and joint hypermobility variable		x							
INVEST: Rectal balloon sensory testing		x							
INVEST: Balloon expulsion test		x							
INVEST: Anal manometry		x							
INVEST: Radio-opaque marker transit study		x							
INVEST: Evacuating proctogram		x							
Randomisation		x							
Surgery assessments (LapMVR) + 30 day post op review.			**Grp 1**	**Grp 2**	**Grp3**				
Standardised outcome framework assessments (PAC-QOL,PAC-SYM, EQ-5D-5L, EQVAS, PHQ9, GAD7, CC-BRQ, BIPQ-CC, VAS, St Marks Continence Score, Sexual function questionnaire[PISQ-12 and MSHQ-EjD])		x	x	x	x	x	x	x	x
Patient Diary/Journal provided		x	x	x	x	x	x	x	
Patient Diary/Journal Collected			x	x	x	x	x	x	x
AE and ConMeds and Health Care utilisation		x	x	x	x	x	x	x	x

*Allow up to 4 weeks for INVEST only radio-physiology assessments between baseline and randomisation if not previously performed. Maximum duration of participation is dependent on arm of study due to difference in wait time for surgery. Minimum 52 weeks, Maximum 76 weeks.

FIGURE 7.5 - STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS (SPIRIT) DIAGRAM.

7.2.7.2. Visit 1 - Consent, screening, and baseline assessments

Visit 1 will be conducted face-to-face in clinic or private research environment. Following a detailed discussion about the trial and review of PIS, basically eligible and agreeable patients will complete written informed consent, followed by screening and confirmation of eligibility for randomisation by structured medical and surgical history and review of physical examination findings. Thereafter, additional baseline outcome assessments will be conducted. These include several key validated assessments that profile patients for important characteristics informing disease pathophysiology and important potential predictors of treatment response. All have been selected on the basis of trade-off between adequate detail and achievable brevity. These instruments will be coalesced into a single booklet (design and presentation have been optimised by patient representatives).

Screening/Confirmation of Eligibility

- Structured medical and surgical history by interview including medication usage.
- Clinical examination findings (carried forward if performed previously within last 3 months): standardised exam of perineum/anus/rectum/vagina including POP-Q assessment of rectocoele.
- Review of clinical radio-physiological investigations (some further tests may be required to meet INVEST standard).
- Final review by pelvic floor MDT (as NHS England draft recommendation) to confirm appropriateness for surgery.

Standardised outcome framework

- PAC-QOL, PAC-SYM, EQ-5D-5L & EQVAS, PHQ9, GAD7, CC-BRQ, BIPQ-CC, St Marks Incontinence score, PISQ-12 for women and MSHQ-EjD Short Form for men).
- Baseline 2-week patient bowel diary and health economics journal will be given.

Other baseline only assessments

- Constipation (2006) and IBS (2006) modules of Rome III questionnaire.
- Cleveland Clinic constipation questionnaire (Agachan et al. 1996).
- Brief, chronic pain, autonomic and joint hypermobility assessments.

Randomisation will be performed only once full eligibility has been confirmed and all baseline assessments taken (which may require INVEST). Urinary pregnancy testing will be made available to women of child-bearing potential at eligibility assessment and advice will be given to all women regarding need to prevent pregnancy during the study intervention period.

7.2.7.3. Visit 2 – Run in for Surgical Interventions

Participants will be randomized (at visit 1) to three arms with different delays before surgery. In all arms there will be a period of 4 weeks post-eligibility to arrange the logistics of surgery (T–4w to T0) and ensure that patients have returned to their normal life routine after various assessments. Subsequently, LVMR will be performed at T0 in group I (Visit 2); T12 (12 weeks) in group II (Visit 3); T24 (24 weeks) in group III (Visit 4).

7.2.7.4. Visits 2-8 - Follow-up outcome assessments

All patients will complete the standardised outcome framework (inclusive of PAC-QOL and PAC-SYM) questionnaires at T–4, T0, 12, 24, 36, 48, 60 and 72 weeks post run in (see Additional file 2). This ensures that 24 and 48 week post-surgery follow up data for the primary and secondary outcomes are collected on all patients, whilst maintaining blinding of group allocation. Thereafter, participants will leave the study and return to 'routine clinical care' as determined within their local NHS institution. During the first 24 weeks post-surgery patients will be quarantined from further intervention, excepting emergency interventions (e.g. for complications).

7.2.7.5. Participant withdrawal (including data collection / retention for withdrawn participants)

Individual participants will be able to drop out at any time of either the treatment or follow up. Data will be retained for intent-to-treat analysis from all participants after the point of consent and recruitment as outlined in the PIS:

a) *Withdrawal from treatment criteria (no further interventions but follow up data collected)*

Participants will be withdrawn from the study interventions if they develop any of the following exclusion criteria:

- becomes pregnant or intends to become pregnant (only in baseline and intervention phases);
- subsequently diagnosed with proven cause for secondary constipation e.g. Parkinson's disease or bowel obstruction;

- develops significant inter-current illness precluding participation;
- develops acute psychological problem causing safety concern;
- elective withdrawal.

b) Loss to Follow Up (no further interventions or follow up data collected)

Participants may be withdrawn from the trial if:

- they become lost to follow up (LTF) after at least 3 failed attempts by research staff to make contact via 2 different methods (e.g. phone and letter);
- participant choses to withdraw and does not wish to participate in follow up data collection;
- death or significant incapacity making follow up data collection impossible.

7.2.7.6. End of study definition

The end of study is defined as the last patient last visit (LPLV). The sponsor, REC and local R&D departments will be informed of end of study and site closure and archiving procedures initiated.

7.2.7.7. Criteria for early termination

If the DMEC, PSC, REC or sponsor determine it is within the best interests of the participants or trial to terminate the study, written notification will be given to the CI. This may be due to, but not limited to; serious safety concerns, serious breaches, acts of fraud, critical findings or persistent non-compliance that negatively affects patient safety or data integrity. If the study is terminated, participants will be returned to the NHS normal follow up and routine care.

7.2.8. Data management

The data collected for the trial will be a mixture of routinely collected data, verifiable against the medical records and patient reported outcome measures (PROMs) or questionnaire data, collected directly to CRF.

Each recruiting site will be required to keep accurate and verifiable source notes in the medical record relevant to each study participants inclusion and continued participation in the study. Data will be collected, transferred and stored in accordance with GCP guidelines and data protection requirements. The PCTU SOPs and study data management plan will define the exact process of data collection, transfer and storage and control of study data.

All patient identifiable data, such as consent forms, screening and identification logs will be stored in the investigator site files in secure locked cabinets and/or offices, accessible only to delegated members of the study team. Secure methods of data transfer will be used to return CRFs to the coordinating site for centralized data entry, monitoring, quality control and compliance. A copy of the CRF will be held at the site in accordance with GCP.

A secure online OpenClinica trial database will be provided by the PCTU to enable remote data entry of CRFs at sites where this is feasible. This database will provide built in data validation checks with quality control checks performed by checking a predefined percentage of CRF data against data entered into the database. In addition, on site monitoring will enable source document verification of records.

The full data set will be collected face-to-face wherever possible to maximise completeness of data. However, to minimize bias, where possible, a blinded researcher

will collect outcome data. Alternatively, the participant will enter outcome data directly to the e-CRF portal for patient reported outcomes (REDCAP). An automated email reminder will be sent to participants to remind them to complete the questionnaires and diaries every 12 weeks. Telephone or postal follow up will be permitted if necessary. At least 3 attempts via 2 different methods (e.g. phone and letter) will be made by research staff to make contact and collect follow up data, after which the participant may be considered LTF if appropriate (see criteria for withdrawal).

7.2.8.1. Confidentiality

Information related to participants will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldecott Principles, The Research Governance Framework for Health and Social Care, and the conditions of Research Ethics Committee Approval.

Identifiable information to be collected from the participants include, full name, DOB and hospital number and contact details at screening. This information will be used to contact participants but will not leave the study site without prior consent. All case report forms will be pseudonymised. The participant's GP will be informed of their participation in the study, but they may opt out at the time of consent.

The trial data will be made available to suitably qualified members of the research team, study monitors and auditors, the REC and regulatory authorities as far as required by law. The participants will not by identifiable with regards to any future publications relating to this study.

7.2.8.2. Record retention and archiving

When the research trial is complete, it is a requirement of the Research Governance Framework and Sponsor Policy that the records are kept for a further 20 years. For trials involving Barts Health Trust patients, undertaken by Trust staff, or sponsored by BH or QMUL, the approved repository for long-term storage of local records is the Trust Modern Records Centre.

Each site will be required to archive local site files and patient identifiable information such as consent forms and screening logs for a period of 20 years. At the end of the 20 year retention period, the Records Management team will alert R&D that the records are due for disposal. The chief investigator and sponsor will be informed and the full agreement of everyone concerned will be obtained before any records are destroyed.

7.2.9. Statistical considerations

7.2.9.1. Sample size

The sample size has been calculated using the primary clinical outcome, a change in mean PAC-QOL score.(Marquis et al. 2005) This widely used, psychometrically robust measure of overall treatment response with concurrent validity to patient global ratings of success has been used by previous trials of behavioural therapies and surgical trials (Gosselink et al. 2013) (including LVMR) in CC.(Dubois et al. 2010) For a chronic condition such as CC, a difference of 1.0 point in the primary outcome (score range = 1-4) can be considered clinically important and also the notional minimum required to justify the cost and invasive nature of LVMR, or of a more complex and expensive treatment.

Previous trials have shown a 1 point decrease in PAC-QOL from pre-operative to 48 weeks (1 year) post-surgery.(Gosselink et al. 2013) Using a stepped-wedge design, we

hypothesize that PAC-QOL score at any time point during follow-up will be approximately 1.0 points lower than pre-operative participants.

Sample size was calculated by simulation using the simsam package in Stata.(Hooper 2013) We assumed PAC-QOL follows a normal distribution over all time points with a standard deviation of 1.5 and with a correlation between repeated assessments equal to 0.5.

Simulation shows that detection of a 1.0 point difference in 6-month PAC-QOL, with 95% power (purposely chosen to reflect the magnitude and risk of intervention) at the 5% significance level, requires 34 participants in each of the three arms. Allowing for a 10% loss to follow up, a sample size of 38 is needed per arm (i.e. a total sample size of 114 patients across the three arms). Should the correlation between repeated assessments be lower than 0.5, a sample size of 114 will still provide at least 90% power for the study. This was calculated using the same simulation procedure with correlations of 0.3 and 0.1.

7.2.9.2. Methods of analysis

7.2.9.2.1. Clinical outcomes

Primary objective

a) Primary outcome

   PAC-QOL scores at the time-points T0, T12, T24, T36 and T48 weeks in the 3 arms will be analysed using a mixed linear regression model, with random effects for participants and a fixed effect of time since randomisation (potentially considering a random effect for time as well to relax the assumption of same time trend for each participant) to estimate mean

differences between PAC-QOL score before and after LVMR. The contrast of primary interest is between the score at 24 weeks after surgery and the score at baseline. Missing data will be imputed through multiple imputation by chained equations.

b) Secondary outcome

PAC-SYM scores will be analysed by the same approach as above.

Secondary objectives

All clinical outcomes derived from the standardised outcome framework will be analysed at 0, 24, 48 and potentially 60 and 72 weeks post-operatively. Outcomes will take the form of count (change in number of symptom episodes), ordinal (patient's global impression of success) and continuous (questionnaire scores) data. Mixed models appropriate to the outcome data types will be fitted to estimate the treatment effect, adjusting for baseline values, gender, and breakthrough medication use as a potential confounder.

All participants randomized to the three groups will be analysed according to their allocation: we would allow for a +/- 2 weeks from the scheduled intervention date: eventual deviations from this time buffer will be taken into account by a modified intention-to-treat analysis.

Analysis will be performed using proprietary software (Stata, Stata Corp. Texas) with $p<0.05$ will be taken to indicate statistical significance.

7.2.9.2.2. Health economic outcomes

Within-trial stochastic analysis will compare the cost/success and cost/QALY of LVMR. Patient-level cost-effectiveness analysis will use standard bootstrapping methods to generate cost-effectiveness acceptability curves exploring value-for-money.

Cost-effectiveness models that extrapolate beyond 3-6 months duration are problematic in adult constipation, as subsequent care and outcomes are contingent upon subsequent care received and the underlying disease process. However, the CapaCiTY programme as a whole provides a unique opportunity to construct probabilistic models exploring optimal pathways from effectiveness and cost-effectiveness perspectives.

Since patients will (within the CapaCiTY programme) be followed along a pathway that includes a series of steps of care, it will be possible to construct costs and outcomes for a range of patient pathways providing comparative longer term cost effectiveness estimates. For example, it will be possible to ask whether INVEST or No-INVEST-led first line care leads to lower overall costs or improved outcomes. Patient-level data from recruitment through the various work packages will be used to construct pragmatic, probabilistic models to explore optimal pathways from effectiveness and cost-effectiveness perspectives.

Analyses from NHS and societal perspectives will be supported by recording relevant resource use during each work package, and a common panel of outcomes. Adjustment for time preference will be at the socially accepted rate for cost effectiveness analyses (currently 3.5% for costs and benefits).

7.2.10. Qualitative interviews

Interviews will be digitally recorded, anonymised, transcribed verbatim and analysed using a pragmatic thematic analysis and NVivo8 software (QSR International Ltd, Warrington, UK) for data management. Data analysis will be developed as outlined by Fereday & Muir-Cochrane 97 in the first instance by mapping key concepts derived from the transcripts ('charting') and extracting emergent themes from the transcripts. Independent analyses will be conducted and resulting codes and themes will be compared and refined in discussion. Emergent themes, together with captured observational data, will form the basis of analytical interpretation.

7.3. Ethical considerations

7.3.1. General

The study will be carried out in accordance with the ethical principles in the Research Governance Framework for Health and Social Care, Second Edition, 2005 and its subsequent amendments and applicable legal and regulatory requirements.

CapaCiTY study 3 is the last of the three trials in the CapaCiTY Programme, all of which have been reviewed by the London – City and East REC. Within the programme, the 3 studies have separate protocols and patient information sheets to be consented separately as if they were distinct entities. This is necessary to limit patient information which would otherwise be over-burdensome. We have discussed the use of sequential consent forms within one pragmatic enriched design with Dr Art Tucker, national ethics advisor and Chair of the East London and the City REC who confirms this will be practicable.

7.3.2. Specific

The protocol has been reviewed by Prof Richard Ashcroft, Professor of Medical Ethics and Law at QMUL. Important considerations that have informed pragmatic design include:

a) Wait-list controlled design: a waiting list control group serves the purpose of providing an untreated comparison for the active treatment group, while at the same time allowing the waiting-listed participants an opportunity to obtain the intervention at a later date. In keeping with the basic ethical tenets of this design (Elliott and Brown 2002), the average wait will be shorter than that for routine services. This is achieved by randomising patients to receive urgent (4 weeks) or routine intervention as opposed to all having routine status as would be normal NHS clinical care. Current waiting times at most included centres are approx. 3-6 months for surgery whereas the mean waiting time in the study will be 3 months. Survey evidence from 100 patients indicates that for a chronic condition such as CC, patients are prepared to accept a randomization strategy that allocates them to a one in three chance of waiting up to 24 weeks for surgical treatment;

b) Limitation of intimate examinations to one time point (not repeated if performed before recruitment);

c) Timings of outcomes: Within the standardised outcome framework, outcomes will be undertaken at fixed intervals of 12 weeks before and after the intervention to 48 weeks follow up within the stepped-wedge study and thereafter in 12 week intervals within the cohort assessments up to 72 weeks.

For a period of 24 weeks follow up post-surgery, patients will not progress to further therapies thus preventing outcome 'contamination'. This 'quarantine' period from major therapy progression is required to give a reasonable clinical impression of outcome. This delay is akin to that in usual NHS care during which general supportive care will be provided while further interventions are considered. Thus, this proposed 'quarantine' period to 6 months confers no disadvantage and may even represent an acceleration of treatment progression. Ethically, this is viewed as a reasonable trade-off for the commitment to the research programme;

d) Recruitment & consent: study 3 represents one of the 3 studies incorporated in the NIHR-funded CapaCiTY programme. Although patients may have moved sequentially through earlier treatments (and therefore studies) during the programme course, study 3 will be consented as a distinct single entity.

The investigating team have no conflicts of interest.

7.4. Safety considerations

7.4.1. Surgery

LVMR has a number of established specific complications in addition to the general risks of surgery. Data on these complications are in the public domain (Zbar et al. 2003) and can be considered to be expected events. These will however still be recorded for outcome reporting.

7.4.1.1. Intra-operative complications

Include inadvertent injury to other intraperitoneal viscera. These are common to all laparoscopic surgery, such as:

- bowel, ureter, bladder or vaginal injuries or perforations;
- vascular or nerve damage.

7.4.1.2. Post-operative complications

- Urinary retention (<10%);
- urinary tract infection;
- worsening of, or *de novo* urinary incontinence;
- port site complications (early or late port site hernia; bleeding or wound infection);
- pelvic sepsis;
- pelvic pain;
- haemorrhage especially from the posterior vaginal wall;
- vaginal or rectal perforation;
- faecal impaction (rare);
- small bowel obstruction;
- sexual dysfunction (rare);
- dyspareunia (uncommon) – usually resolves with time (Wong et al. 2011);
- osteomyelitis of the sacrum and spondylodiscitis (Probst et al. 2014);
- venous thromboembolism.

7.4.1.3. Prosthesis-related complications

- Minor mesh complications;

- mesh infection (<3%);
- mesh erosion (<3%);
- mesh sinus.

Minor mesh complications can be managed by local measures including suture sinus removal, mesh trimming, performed endo-rectally or endo-vaginally with subsequent healing. Major mesh complications include (1) generalised mesh sepsis requiring mesh removal endo-rectally or trans-abdominally or both, with or without partial or complete rectal excision; (2) rectovaginal fistula also requiring mesh removal endo-rectally or trans-abdominally or both +/-partial or complete rectal excision.

7.4.2. INVEST safety considerations

Patients undergoing INVEST-guided therapy will have two radiological procedures (whole gut transit study and barium defaecography) using ionising radiation as outlined above. The combined dose of these procedures (~1.2mSv) is equivalent to less than 7 months annual background radiation dose from living in the UK (this has been recertified by Barts Health NHS Clinical Physics Department based on doses from 20 equivalent procedures). Further, these investigations would be carried out in routine clinical practice in many centres for patients at the same point as recruitment to this study.

7.4.3. Insurance and indemnity

In the event that something does go wrong and patients are harmed during the research and this is due to someone's negligence then they may have grounds for legal action against the sponsor Queen Mary, University of London, but they may have to pay their legal costs. Insurance and indemnity is provided by the sponsor.

7.4.4. Safety reporting

Serious Adverse Event (SAEs) that are considered to be 'related' and 'unexpected' are to be reported to the sponsor within 24 hours of learning of the event and to the REC within 15 days in line with the required timeframe. The CI will send the Annual Progress Report to the REC and to the sponsor.

7.4.4.1. Expected SAE's

The following SAEs are expected to occur rarely in this patient population and will not be reported:

- Hospital admission for exacerbation of constipation symptoms including impaction.
- Hospital admission for unrelated elective surgical procedures or accidental injury.
- Prolongation of hospitalisation due to complications from surgery.

7.4.4.2. Urgent safety measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical trial subjects from any immediate hazard to their health and safety. The measures should be taken immediately. In this instance, the approval of the REC prior to implementing these safety measures is not required. However, it is the responsibility of the CI to inform the sponsor and Main Research Ethics Committee (via telephone) of this event immediately.

The CI has an obligation to inform both the REC in writing within 3 days, in the form of a substantial amendment. The sponsor (Joint Research Management Office [JRMO]) must be sent a copy of the correspondence with regards to this matter.

7.4.4.3. Overview of the safety reporting responsibilities

The CI/PI has the overall pharmacovigilance oversight responsibility. The CI/PI has a duty to ensure that safety monitoring and reporting is conducted in accordance with the sponsor's requirements (Figure 7.6).

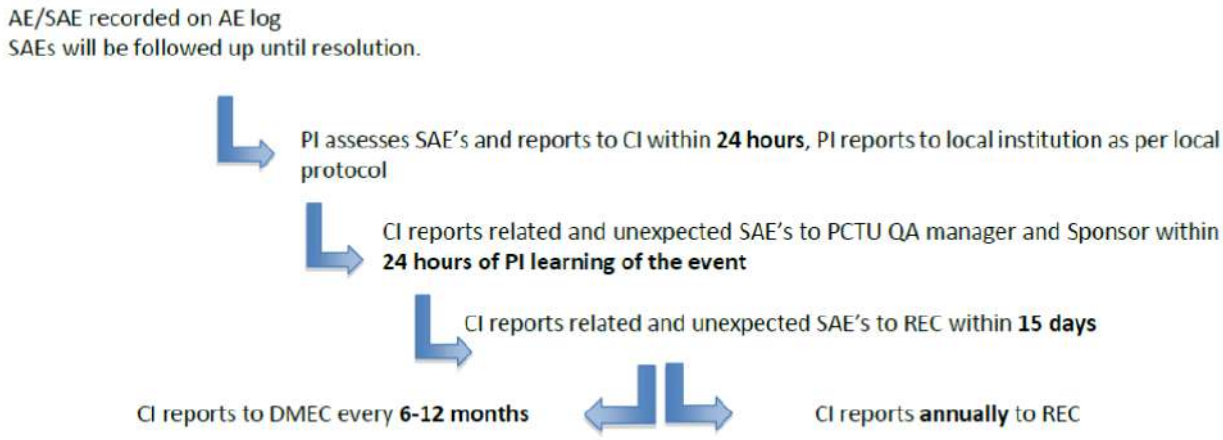

FIGURE 7.6 - COMMUNICATION ORGANOGRAM FOR REPORTING SERIOUS ADVERSE EVENTS.

7.5. Monitoring and auditing

7.5.1. Risk assessment

The PCTU quality assurance manager will conduct a study risk assessment in collaboration with the CI. Based on the risk assessment, an appropriate study monitoring and auditing plan will be produced according to PCTU SOPs. This monitoring plan will be authorised by the sponsor before implementation. Any changes to the monitoring plan must be agreed by the PCTU QA manager and the sponsor.

A study may be identified for audit by any method listed below:

- a project may be identified via the risk assessment process;
- an individual investigator or department may request an audit;

- a project may be identified via an allegation of research misconduct or fraud or a suspected breach of regulations;
- projects may be selected at random. The Department of Health states that Trusts should be auditing a minimum of 10% of all research projects;
- projects may be randomly selected for audit by an external organisation.

Internal audits may be conducted by a sponsor's or funder representative.

7.5.2. Quality assessment of LVMR

Monitoring and quality control will be conducted remotely via video submission and assessed against the standardised LVMR protocol and assessment criteria (see Additional file 8). Monitoring will be taking the form of planned, random and triggered sessions.

7.5.2.1. Planned monitoring

All PIs must record and submit the unedited and anonymised video of the LVMR performed in the first patient enrolled in the CapaCiTY study 3. Each video will be allocated to two peer reviewers of a 3-member expert panel. Based on blinded assessment of unedited and anonymised videos by experts' review, the panel will decide whether the PI is 'adherent' to the standardized technique. Any disagreement will be solved by consensus after consulting a third independent expert. If deemed 'non-adherent' to the standardized technique, the site will be notified that a step needs to be corrected. The PI must submit the unedited and anonymised video of the LVMR performed in the second patient enrolled in the CapaCiTY study 3. In case of 'failure' to comply with the standardized surgical technique for LVMR or following a second

judgment of 'non-adherence' to the standardized technique, this will trigger an onsite training and monitoring session for the site. Monitoring will continue until adherence is achieved. Or a third 'non-adherence' or second 'failure' will result in withdrawal of the site/PI from the study.

7.5.2.2. Random monitoring

All PIs must record and submit the unedited and anonymised video of the LVMR performed in a randomly selected patient enrolled in the CapaCiTY study 3 (1 in 5 at site level). The adherence to the standardized technique will be established by consensus as described for the planned monitoring.

7.5.2.3. Triggered monitoring

The DMC will review the morbidity and mortality rates, adverse and serious adverse events from all sites. Safety concerns may trigger additional monitoring or on-site training and mentorship visits to take place by expert panel. Repeated 'nonadherence' or 'failure' to comply will result in PI and site withdrawal.

7.6. Devices and licenses

7.6.1. Devices

The following is a list of all devices used. None are specific to the research itself and all are currently used in routine clinical practice. All are CE marked and approved for use in the UK.

a) Disposable proctoscope (supplier as local NHS practice). This will be commonly be used as part of clinical examination at baseline and is also used to introduce barium paste into the rectum during INVEST;

b) high-resolution anorectal manometry catheters and rectal balloons for anal manometry / rectal sensory testing: various suppliers (part of INVEST – see above);

c) balloon catheters for balloon expulsion test (part of INVEST – see above);

d) radio-opaque markers for colonic transit study: various suppliers (part of INVEST – see above);

e) standard departmental X-ray equipment including radiolucent commode for defaecography (part of INVEST- see above);

f) surgical instrumentation including disposable and reusable instruments;

g) mesh:

- Synthetic: titanium-coated light weight polypropylene;
- Biologic: Strattice, Permacol;
- Mixed: biologic and synthetic;

h) suture material: any; usually long-term absorbable material e.g. PDS.

7.6.2. Licenses

Most of the questionnaire-based tools are free to use within the public domain. The permissions / licenses to use all instruments will be sought with finance where required:

- PAC-QOL score: MAPI registered;
- PAC-SYM score: MAPI registered;
- MSHQ-EjD: MAPI registered;
- EQ-5D-5L: registered.

No costs are associated with the following tools:

- Depression, anxiety and somatisation modules of the Patient Health Questionnaire;
- Illness perception questionnaire;
- Composite Rome III / Cleveland Clinic constipation questionnaire;
- Brief, chronic pain, autonomic and joint hypermobility;
- Negative perfectionism;
- Avoidant and 'all or nothing' behaviour subscales of the behavioural response to illness questionnaire.

7.7. Trial management

Each participating centre will identify a site specific PI who will nominate a local contact for that centre (this may be him/herself). The PI and local contact will:

- be familiar with the trial;
- liaise with the PMG;
- ensure that all staff involved in the trial are informed about the trial and have received requisite training;
- ensure that mechanisms for recruitment of eligible participants, including the availability of participant information and data collection tools, are in place;
- monitor the effectiveness of data collection tools and participant information and discuss the reasons for non-recruitment with relevant staff;
- ensure site staff collect necessary trial data and perform quality checks;
- notify the CI of any SAEs and serious breaches within required timelines;
- make data available for verification, audit and inspection processes as necessary;

- respond to requests for documentation and data required for centralised monitoring;
- ensure that the confidentiality of all information about trial participants is respected by all persons.

Site initiation will be conducted with each site. This will include training in the trial protocol and standard operating procedures, such as data collection, randomisation and taking informed consent. Evidence of appropriate training, local approvals and essential documentation will be required before participants being enrolled at each site. Training will be documented on training logs.

7.7.1. Trial committees

The project will be under the auspices of the Chief Investigator and the PCTU. The project will be overseen by a Programme Steering Committee (PSC).

The composition and responsibilities of the PSC will comply with the NIHR guidance and PCTU SOP on Trial Oversight Committees. The role of the PSC is to provide overall supervision of the study on behalf of the sponsor and funder to ensure the study is conducted in accordance with the principles of Good Clinical Practice (GCP) and relevant regulations.

The responsibilities of the PSC will include:

- ensuring that views of users and carers are taken into consideration;
- advising on the trial protocol;
- advising on changes in the protocol based on considerations of feasibility and practicability;

- assist in resolving problems brought to it by the PMG;
- monitor the progress of the trial and adherence to protocol and milestones;
- consider new information of relevance from other sources;
- consider and act on the recommendations of the data monitoring and ethics committee (DMEC), sponsor and/or REC;
- review trial reports and papers for publication.

The PSC will meet to review the protocol before the start of the programme and then soon after the first participants are recruited and either meet or teleconference every 6 months thereafter throughout the lifetime of the programme.

Representatives of the Trial Sponsor and Funder will be invited to attend.

A PMG will meet monthly initially during study set up and then less frequently, every 2 months. The PMG will be responsible for day-to-day project delivery across participating centres and will report to the PSC. The PMG will be responsible for monitoring adherence to the study timelines and expected recruitment rates. Regular reports will be produced to enable deviations from the project plan to be identified and contingencies planned, discussed and executed in a timely fashion (Figure 7.7).

A data monitoring & ethics committee (DMEC) will be convened. A DOMACLES (DAta MOnitoring Committees: Lessons, Ethics, Statistics) charter will be adopted, and the project team will provide the DMEC with a comprehensive report, the content of which should be agreed in advance by the Chair of the DMEC and follow guidelines set out in the charter. The DMEC will meet at least four weeks prior to the PSC to enable recommendations to be fed forward.

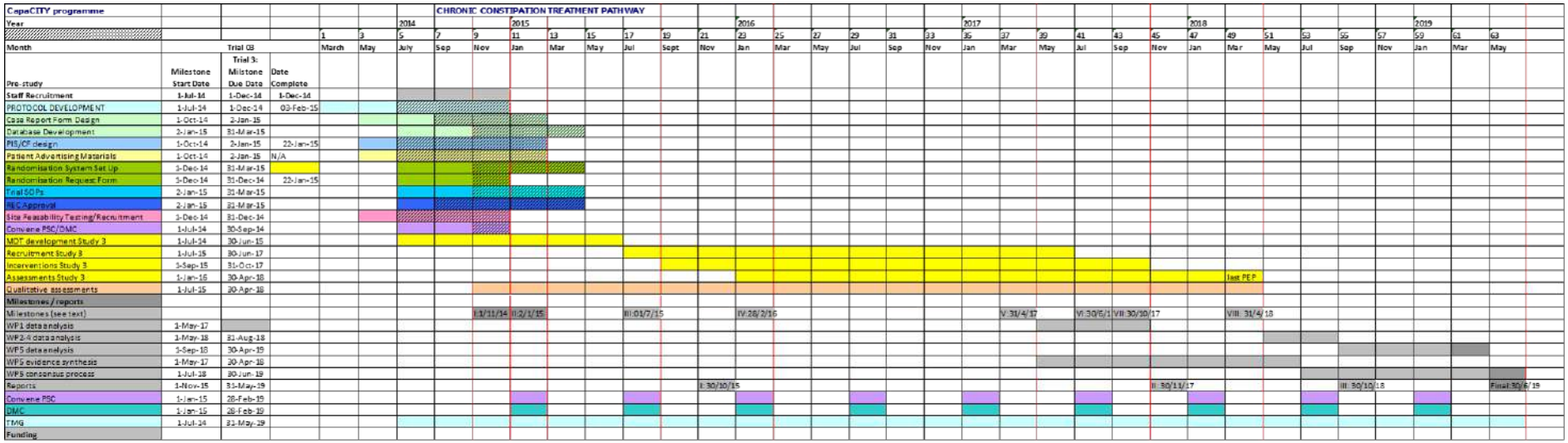

FIGURE 7.7 - CAPACITY STUDY 3 GANTT CHART.

A constipation research advisory group (CRAG) will be formed as part of a well-developed patient and public involvement (PPI) strategy at QMUL (in close association with the charity Bowel and Cancer Research). This advisory group will comprise 8 patients and 2 lay members derived from London and Durham. This group will have geographical diversity (North and South) and a disease-appropriate demographic (8 females, 2 males). The CRAG will review participant information sheets, booklets, diaries and advertising/marketing materials, provide lay representation on the PSC, conduct parallel qualitative analysis, produce lay summaries for dissemination of results, present at local research events and conduct patient focus groups and workshops.

7.8. Discussion

An individual level stepped-wedge randomised trial serves the purpose of providing an untreated comparison for the active treatment group, while at the same time allowing the waiting-listed participants an opportunity to obtain the intervention at a later date. In keeping with the basic ethical tenets of this design, the average waiting time for LVMR (12 weeks) will be shorter than that for routine services (24 weeks). We acknowledge that availability of beds may represent a major bane for this trial. However, we have attempted to overcome this by allowing a 4 weeks run in post-eligibility to arrange the logistics of surgery and a 2-week tolerance interval from the scheduled intervention date.

Chapter 8 - Conclusions and future research

Controversies exist in the diagnostic and therapeutic approach to chronic constipation (CC) in adults. In those with an evacuation disorder, significant disagreement has been shown between current diagnostic modalities in the assessment of functional and structural abnormalities. In Chapter 2, data obtained by blinded multi-observer assessment, and in a relatively large sample size, suggest that the interpretation of anorectal manometry patterns is reproducible. However, nearly 90% of healthy volunteers have a pattern that is currently regarded as 'abnormal'. Hence, anorectal manometry is of limited utility for diagnosing dyssynergic defaecation.

Moreover, both the balloon expulsion test and anorectal manometry, considered by many as index investigations, provide extremely limited information on anatomical obstructive features. Conversely, through systematic review and meta-analysis (see Chapter 3), defaecography was confirmed to provide a more thorough assessment of both functional and structurally pathological features and should thus be considered the first-line diagnostic test, if resources allow.

Using rigorous methodology with solid definitions and cut-offs derived from studies on healthy subjects (meta-analysed in Chapter 3), we systematically reviewed defaecographic phenotypes in a large series of CC patients, providing phenotypic characterization of the largest series ever reported of male patients with moderate to severe symptoms of constipation (see Chapter 4). Our analysis has shown that multiple structural and functional abnormalities may coexist in the same subject, with degree of

overlap greater than previously recognized. Coexistence of structural abnormalities was significantly more often encountered in females, reflecting global pelvic floor weakness.

The clinical utility of other less invasive radiological tools (e.g. pelvic floor ultrasonography combining transperineal, endovaginal and endoanal scanning) should be investigated in well-designed diagnostic accuracy studies with defaecography as reference standard. Ultimately, ultrasonography might serve as screening method prior to defaecography.

A systematic review of evidence for the perioperative and long terms benefits and harms of rectal suspension procedures identified no high quality studies (see Chapter 5). The evidence base is characterised by observational studies of variable and often uncertain methodological quality. Definitions are poor, e.g. grading of complications was inconsistent. The difficulties in conducting randomized controlled trials (RCTs) for complex interventions such as surgery are well rehearsed (Ergina et al. 2009), but their importance is exemplified by recent sacral neurostimulation RCTs (Dinning et al. 2015, Zerbib et al. 2017) that directly contradict observational data. While it can be argued that sham surgery would be difficult to justify for patients with a chronic debilitating condition, it is disappointing that no level I evidence has been produced to compare classes of procedure where more than one is appropriate. Such comparison trials of different techniques may face problems of equipoise and interventional fidelity, and might need to overcome a specialty divide, e.g. posterior repair vs. transanal repair of rectocoele (the former performed largely by gynaecologists or female urologists and the latter by colorectal surgeons). An alternative is waiting-list designs where the wait time for surgery can be randomized and analysis-based on longitudinal outcomes before and

after intervention (McCulloch et al. 2009). An example of such a study is the CapaCiTY03 stepped-wedge RCT of laparoscopic ventral mesh rectopexy (LVMR) in adults with CC (see Chapter 7).

In Chapter 6, a large single-centre retrospective cohort study (of prospectively collected data) assessed clinical outcomes and predictors thereof in 537 patients undergoing LVMR for internal rectal prolapse. The main results demonstrated significantly reduced constipation and incontinence symptoms following surgery and improvements in disease specific quality of life that were maintained to last follow-up. Older age and previous urogenital prolapse surgery were independently associated with poorer quality of life at 12 months. Mesh type was significantly associated with mesh complication-free survival: polypropylene and titanium-coated lightweight polypropylene (TCLP) had better survival than polyester (HR 0.25 [95%CI0.11-0.54], 0.31 [95%CI0.09-1.06], respectively). Mesh type was strongly predictive of time to recurrence of prolapse, with polypropylene having the best recurrence-free survival, and TCLP the worst (HR 0.07 [95%CI0.02-0.34] vs. 2.93 [95%CI1.31-6.55], respectively).

Accepting the difficulty in performing RCTs, there is still much opportunity to improve the evidence base by encouraging high quality observational studies. Prospective cohort studies could benefit from incorporating some of the scientific rigor of RCTs to limit obvious sources of bias e.g. by multicentre recruitment and use of blinded observers to collect outcomes. Awareness of reporting standards by authors and journals may in turn feed better protocol-driven research (von Elm et al. 2007). They should incorporate the few validated patient-reported outcome measures (PROMS) that are available, e.g. PAC-QOL and PAC-SYM, internationally-accepted HR-QOL measures e.g. EQ-5D-5L and

monitor harms in a systematic manner using established systems e.g. Clavien-Dindo (Ergina et al. 2009). They should also consider collecting health utilization data from patient information systems, the importance of which is illustrated by the Dudekula study (Dudekula et al. 2015) of colectomy. Outcomes should be reported back to an independent 3rd party rather than the surgeon who performed the operation (Tillin et al. 2006).

A UK RCT is underway to evaluate LVMR (see Chapter 7). A further RCT is however recommended to determine outcomes of repair of large rectocoele (in isolation), comparing posterior repair of the vagina vs. transanal repair. It is acknowledged that this might require an expertise-based design (Devereaux et al. 2005, Ergina et al. 2009) but it is an unanswered question for the indication of CC or obstructed defaecation. Systematic review data would also support a randomized comparison of stapled transanal rectal resection (STARR) with rectopexy for patients with high-grade intussusception and rectocoele. However, expert opinion suggests that STARR is no longer popular. An alternative would be to perform a prospective cohort study capturing all current practice or to recruit to a series of RCTs from a single large cohort using Trials within Cohorts (TWiCS) methodology (Relton et al. 2010). This could be performed internationally but might also be possible in a large single country if all 3 main classes of procedure are still commonly utilized.

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