Managing Low Anterior Resection Syndrome and Optimizing Quality of Life following Rectal surgery

Jessica Holland
Experimental Surgery Department, McGill University, Montreal

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1 Preface

1.1 Thesis format:

This manuscript-based master's thesis has been written according to the guidelines and specifications of the McGill Department of Graduate and Postdoctoral studies. It contains two distinct manuscripts which are in preparation for publication. The first manuscript is a systematic review, entitled "A Systematic Review of the impact of Transanal Irrigation on the symptoms of Bowel Dysfunction following Rectal Resections in adults", that has been prepared for submission to a colorectal focused journal. The second manuscript consists of a protocol for an ongoing randomized controlled trial, entitled "Transanal Irrigation for the Management of Low Anterior Resection Syndrome (LARS): A Multicenter Crossover Randomized Controlled Trial", which has been prepared for submission to the British Medical Journal Open.

1.2 Acknowledgments

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Each manuscript lists the individual contributors who have contributed to these works, and they have all also provided general support for my ongoing research on Low Anterior Resection

Syndrome. I will be forever indebted to the whole clinical team at the Montreal General Hospital and the Jewish General hospital for their support, instruction, and knowledge.

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1.3 Contributions of Authors

I, Jessica Holland, attest that I have contributed as the primary author for the conception, design, data collection, analyses and writing of all the work contained in this master's thesis.

1.3.1 Manuscript 1: Authors

Dr. Jessica Holland, BSc. MD, McGill University, Department of Colorectal Surgery, Montréal, QC.
Dr. Natasha Caminsky, BSc MSc MD, McGill University, Department of Colorectal Surgery, Montréal, QC.
Dr. Carol-Ann Vasilevsky, MDCM, Director of the Division of Colon and Rectal Surgery Jewish General Hospital, McGill University, Department of Colorectal Surgery, Montréal, QC.
Dr. Nancy Morin, MD, McGill University, Department of Colorectal Surgery, Montréal, QC.
Dr. Allison Pang, MSc MD, University, Department of Colorectal Surgery, Montréal, QC.
Dr Marylise Boutros, MD, McGill University, Department of Colorectal Surgery, Montréal, QC.

1.3.2 Manuscript 2: Authors

Dr. Jessica Holland, MD, McGill University, Department of Colorectal Surgery, Montréal, QC
Dr. Shafic Abdulkarim, MD, McGill University, Department of Colorectal Surgery, Montréal, QC
Dr. Gordon Best, MD, Ottawa Hospital, University of Ottawa, Ottawa, ONT.
Sarah Saboobeh, Jewish General hospital, Diviesion of Colorectal Surgery, Montréal, QC
Marie Demain, Jewish General hospital, Diviesion of Colorectal Surgery, Montréal, QC
Dr. Sahir Bhatnagar, PhD, Department of Epidemiology, Biostatics and Occupation health and the Department of Diagnostic Radiology, McGill University

Dr. Alexander Sender Liberman, McGill University, Department of Colorectal Surgery, Montréal, QC
Dr. Carol-Ann Vasilevsky, MDCM, Director of the Division of Colon and Rectal Surgery Jewish General Hospital, McGill University, Department of Colorectal Surgery, Montréal, QC
Dr. Nancy Morin, MD, McGill University, Department of Colorectal Surgery, Montréal, QC
Dr. Allison Pang, MSc MD, McGill University, Department of Colorectal Surgery, Montréal, QC
Dr. Sami Ahmed Chadi, MD MSc, Toronto Western Hospital, University Health Network
Dr Sébastien Drolet, Hôpital Saint-François d'Assise, Centre de Recherche de Québec, Montréal OC
Dr. Husein Moloo, MD MSc, Ottawa Hospital, University of Ottawa, Ottawa, ONT.
Dr. Carl Brown, MD MSc, St Paul's Hospital, University of British Columbia, Vancouver, BC
Dr Marylise Boutros, MD, McGill University, Department of Colorectal Surgery, Montréal, QC

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1.5 List of Abbreviations

- CCFIS Wexner/Cleveland Clinic fecal Incontinence score
- CIUSSS Centre Intègre universitaire de santé et de services sociaux
- CRC Colorectal Cancer
- HCP Health care providers
- MSK BFI Memorial Sloan Kettering Bowel Function instrument
- LAR Low Anterior Resection
- LARS Low Anterior Resection Syndrome
- LR Local Recurrence
- ODS Obstructed defaecation syndrome (ODS)
- OS Overall Survival

- QoL Quality of Life
- RCT Randomized controlled trial
- RoB Risk of bias
- TAI Transanal Irrigation
- TME Total mesorectal excision
- EORTC-QLQ-C30 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30

2 Abstract / Resumé

2.1 Abstract

Introductions: Low Anterior Resection Syndrome (LARS), the bowel dysfunction that results from rectal surgery, has been correlated with a decrease in long-term quality of life (QoL) for rectal cancer survivors. Its current treatment options are limited. Transanal irrigation (TAI) is a non-surgical therapy which can be offered to patients whose LARS symptoms persist despite conservative measures. This thesis presents a systemic review of the evidence for the use of TAI to manage LARS and subsequently proposes a protocol for a cross-over randomized controlled trial (RCT) to address gaps in the current evidence.

Methods: A systematic review of the medical literature on adults who use TAI to manage the bowel dysfunction that follows rectal surgery was conducted. The search was exhaustive, including four major medical databases, grey literature and national clinical registries. All relevant studies were included, apart from single case reports and case series containing less than 10 participants. The primary outcome of interest was the impact of TAI on bowel dysfunction, and secondary outcomes include any change in QoL, side effects, complications, and participant satisfaction with the therapy. Results were reported qualitatively due to the lack of single common outcome measure.

Given the lack of high-quality evidence for the use of TAI, we designed a cross-over RCT to investigate the impact of TAI on QoL, as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30), and bowel dysfunction, as measured by the LARS score and the Cleveland Clinic Fecal Incontinence Score (CCFIS), as well as patient satisfaction with TAI.

Results: The review identified 9 studies and 3 abstracts which addressed use of TAI for the management of LARS. A total of 290 participants were included from across these trials, with a median of 18 participants per trial. The irrigations were performed in most trials using one of two commercially available kits with a cone or balloon catheter on a daily basis or every other day, with a volume starting at 1 liter and adjusted to individual participants' tolerance. A change in LARS score was reported in six trials, all demonstrating a significant improvement in the score. The remaining studies used various bowel function scoring systems or measures of patient

satisfaction. The outcome of the subjective measures of satisfaction were more variable with 40 to 100% of participants reporting success with TAI. QoL measures were reported in four trials with inconsistent findings, but all reported improvement in various individual domains, as measured by different scoring systems. All observational studies were at serious risk of bias, and the single RCT was of suboptimal quality. No meta-analysis was possible due to the lack of a common outcome measure and heterogeneity in the studies.

The purposed RCT detailed in the thesis will address the lack of high-quality evidence for the use of TAI in LARS. It is a multi-center trial which aims to recruit 66 adult participants who have undergone a rectal resection and have persistent major or minor LARS despite conservative measures at least 6 months after their surgery. Participants will be randomized to either 3 months of irrigation, 1 month washout out and then 3 months of control with their current treatment, or the reverse. The impact of TAI will be assessed using patient centered outcome measures, through both qualitative and quantitative questionnaires.

Conclusions: TAI is a promising potential treatment for LARS, but there are significant limitations in the current literature identified in this systematic review and further investigation is warranted as detailed in the accompanying RCT protocol.

2.2 Resumé

Introductions: Le Syndrome de Résection Antérieure Basse (SRAB) est un syndrome définit par une dysfonction intestinale suivant une chirurgie rectale. Il est associé avec une diminution de la qualité de vie à long-terme des survivants du cancer du rectum. De plus, les traitements existants sont limités. L'irrigation trans-anale (ITA) est un des seuls traitements non-chirurgicaux disponible pouvant être offert aux patients présentant des symptômes persistants de SRAB malgré l'usage de mesures conservatrices. Cette thèse présente une revue systématique de l'évidence disponible pour l'usage de l'ITA dans le traitement du SRAB, puis propose un protocole d'essai randomisé contrôlé (ERC) avec croisement pour adresser les lacunes existantes dans l'évidence courante.

Méthodes: Une revue systématique de la littérature médicale étudiant les adultes qui utilisent l'ITA pour gérer les symptômes de dysfonctions intestinales suivant une chirurgie rectale a été menée. L'étude est exhaustive et inclue une recherche de publications dans quatre bases de données majeures, dans la littérature grise, et dans les registres cliniques nationaux. Toutes les études pertinentes ont été incluses, sauf les rapports de cas et les séries de cas incluant moins de dix participants. Le résultat primaire d'intérêt est l'impact de l'ITA sur le dysfonctionnement intestinal. Les résultats secondaires incluent tous changements dans la qualité de vie ainsi que les effets secondaires, les complications, et la satisfaction des participants associé à la thérapie. Les résultats ont été reportés qualitativement à cause du manque d'une unité de mesure commune à travers les études incluses.

Étant donné le manque d'évidence de haute qualité pour l'usage de l'ITA, nous avons conçu un ERC avec croisement pour étudier l'impact de l'ITA sur la qualité de vie des patients, mesurée par le Questionnaire sur la Qualité de Vie Core30 de l'Organisation Européenne pour la Recherche et le Traitement du Cancer (EORTC-QLQ-C30); sur la dysfonction intestinale, mesurée par le Score du SRAB et par le Score d'Incontinence Fécale de la Cleveland Clinic (CCFIS); ainsi que sur la satisfaction des patients avec l'ITA.

Résultats: Cette revue a identifié 9 études et 3 abstraits adressant l'utilisation de l'ITA pour la gestion du SRAB. Un total de 290 participants ont été inclus à travers ces publications avec une médiane de 18 participants par étude. Dans la majorité de ces essais cliniques, les irrigations étaient

performées avec un de deux kits disponibles commercialement, avec un cathéter en cône ou en ballon. Les irrigations étaient performées à chaque jour ou deux et avec un volume initial d'un litre ajusté à la tolérance de chaque participant individuel. Six études ont utilisé le score du SRAB comme mesure principale et ont toutes démontré une amélioration significative du score. Le reste des études ont reporté leurs résultats en utilisant plusieurs systèmes différents de classifications ou de mesures de satisfactions du patient. Le résultat des mesures subjectives de satisfaction étaient plus variables, entre 40 et 100% des participants reportant un succès avec l'utilisation d'ITA. Les mesures de qualité de vie ont été reportées dans quatre essais avec des résultats inconsistants. Cependant, tous ont reporté une amélioration dans plusieurs domaines mesurés par les différents systèmes de scores. Toutes les études observationnelles avaient un risqué élevé de biais, et la seule ERC était de qualité suboptimale. Aucune méta-analyse n'était possible dû au manque d'une unité de mesure commune et dû à l'hétérogénéité des études.

Le but de l'ERC détaillée dans cette thèse abordera le manque d'évidence de haute qualité pour l'usage de l'ITA dans le SRAB. Il s'agit d'une étude multicentrique aillant pour but de recruter 66 participants adultes ayant subi une résection rectale et présentant des symptômes persistants, mineurs ou majeurs, de SRAB en dépit des mesures conservatrices au moins 6 mois après leur chirurgie. Les participants seront randomisés à deux protocoles; 3 mois d'irrigation, 1 mois de délavage et 3 mois de contrôle avec leur traitement actuel, ou le protocole inversé. L'impact de l'ITA sera évalué en utilisant des mesures de résultats centrés sur le patient, à travers des questionnaires qualitatifs et quantitatifs.

Conclusions: L'ITA est un traitement prometteur pour le traitement du SRAB. Cependant, des limitations significatives dans la littérature courante ont été identifiées dans cette revue systématique. Plus d'investigations sont requises et seront potentiellement comblées par le protocole d'ERC ci-joint.

3 Introduction

Rectal Cancer

Colorectal cancer (CRC) is the third most common cancer in Canada, and more than 25 000 Canadian will be diagnosed this year (1). While the overall rate of CRC has declined, the incidence in younger Canadians, specifically those less than 50 years old, appears to be increasing (2). This troubling trend has also been seen in a number of countries worldwide including the United States, Australia, Japan and some European countries without a generally accepted understanding of the etiology behind the rise (3). Rectal cancer appears to be following a similar trend, with some studies reporting an even greater increase in incidence rates in this subset of CRC (3). Fortunately, the treatment of rectal cancer has become increasingly successful, with improved overall survival (OS) rates and decreasing rates of local recurrence (LR) (4, 5). Modern medical and surgical techniques have transformed previously dismal prognosis to an often-curable ailment with a combination of surgery, radiation, and chemotherapy. However, as the management of rectal cancer improves, so does the level of complexity in decision making around the appropriate treatment strategies.

The principle of the total mesorectal excision (TME) for the treatment of rectal cancer was first recognized as early as 1908 by Sir Ernest Miles, who advocated for removal of the mesentery along with the rectum in a combined abdominoperineal resection (APR), which removed the entire anus and rectum along with its associated lymphatic drainage (6). Between 1940 to 1950, the restorative proctectomy was popularized, allowing the restoration of gastrointestinal continuity. This came about as a five centimeter distal margin below the tumour was proven to have comparative survival to the traditional APR (7). In the 1980s, Dr RJ Heald popularized sharp dissection in the ‘holy plane’, preserving the mesorectal fascia, as one of five surgical principles for an oncologic restorative proctectomy, which resulted in a dramatic reduction in LR (8). The rate of LR was further reduced to approximately 5% at 10 years with the introduction of neoadjuvant radiation to the pelvis, combining sensitizing chemotherapy with radiation and TME surgery (9, 10). Recent and ongoing trials are still attempting to characterize the optimal combination of systemic chemotherapy, radiation, and surgery to further minimize LR, maximize OS and minimize the side effects of these combined treatments (11).

As OS improved and LR have fallen, clinicians are increasingly able and motivated to offer restoration of intestinal continuity. For many patients avoiding a permanent stoma, the restoration of intestinal continuity is of primary importance. When asked, patients have expressed willingness to compromise the rate of cure and long-term survival to avoid the creation of a permanent stoma (12, 13). Pathologic evidence has demonstrated that the majority of rectal cancer has limited intramural spread, leading clinicians to accept small distal margins if it allows for sphincter-preservation (14, 15). Classification systems, like Rullier's, has been introduced to describe the tumour relationship with the sphincter complex and suggest that an APR is only absolutely required for frank invasion of the external sphincter (16). For anything less, a partial or total intersphincteric dissection might be attempted with a coloanal anastomosis. This has led to the creation of a number of sphincter-sparing techniques for lower and lower tumours including transanal TME (TaTME). Unfortunately, this aggressive approach to restoration of intestinal continuity can lead to dismal post-operative bowel function due to the combination of the removal of the rectal reservoir, damage to the pelvic musculature, radiation induced changes and compromise of the anal sphincter (17).

Low Anterior Resection Syndrome

Low anterior resection syndrome (LARS), or Anterior resection syndrome (ARS), was introduced as pragmatic term to describe the bowel dysfunction that commonly results from rectal cancer treatment (17). LARS is characterized by a constellation of symptoms, including urgency, incontinence, evacuatory dysfunction and constipation. The first year of symptoms are the most severe, but symptoms persistent after one year are likely to be long-term and may be lifelong (18, 19). As such, LARS has a significant negative impact on the Quality of Life (QoL) of survivors long after treatment has been completed (18).

In an effort to obtain a reproducible and quantifiable measure of LARS symptoms, a group in Denmark developed the LARS score in 2012 as a five-item questionnaire (20). They identified what they 5 most important symptoms of LARS (incontinence for flatus, incontinence for liquid stool, frequency, clustering, and urgency), gave each a question with an individual score, and then combined them to give a composite LARS score (0-42) with three designations for severity: no LARS (0-20), minor LARS (21-29), and major LARS (30-42). The LARS score is currently the most widely-used and validated tool to measure bowel dysfunction after LAR. It

has been since been translated into over 35 languages and validated in at least 14 populations (21). However, the LARS score is limited in its ability to capture the practical impact of symptoms and the consequences of these symptoms on patient's lives. As such, a newer more comprehensive definition of the syndrome is being introduced, which includes 8 symptoms and 8 consequences, but it is to date without a simple reproducible validated instrument to measure it (21). Until one is introduced and adopted, the LARS score remains the most common current instrument for research on this condition.

While the majority of patients will experience some changes in their bowel function following surgery, 48 to 70% of patients will experience significant enough changes to have some degree of LARS, and 36 - 47% will have severe enough symptoms to be classified as major LARS (18, 22, 23). The impact on LARS on QoL has been investigated in a number of studies demonstrating a correlation between increasing LARS score and worsening QoL across a number of domains. Major LARS has demonstrated a 10% reduction in global QoL as measured by the EORTC-QLQ-C30 questionnaire over no or minor LARS (22). Patients with major LARS were also more likely to experience financial difficulties (22). Studies in other geographic populations have supported the correlation of increased LARS score associated with a reduction in the six function subscales of EORTC-QLQ-C30 (23, 24). In a United Kingdom study, 85% of respondents report their bowel function impaired their QoL, and the largest impact was seen in the role and social functioning (25).

There are several known risk factors for LARS, including pre-operative bowel function, tumour characteristics and treatment factors. The more distal the tumour, the more complete rectal resection required, and the lower anastomosis construction required to restore intestinal continuity, all of which will result in a more significant post-operative dysfunction, especially if there is a requirement for total or partial intersphincteric resection (25).There are some techniques in the construction of the anastomosis, such as a side to end anastomosis and colonic pouch, that have been proven to reduce frequency of bowel movement in the first 18 months post-operatively, but there is no current evidence of any long-term benefit (25, 26). Neoadjuvant radiation also results in worse post-operative function, due to worsening compliance and sensory function, as well as increasing risk of post-operative complications such as anastomotic leak (27). Adjuvant radiation has an even more significant impact on and has largely fallen out of

practice as a result (28). Avoiding neoadjuvant radiation in patients with favourable tumour characteristics, such as those detailed in the MERCURY and Quicksilver trials, will avoid the exacerbating effects of radiation of LARS without compromising oncologic outcomes (29-31). Furthermore, the prolonged presence of a diverting loop ileostomy has also been shown to be a potential contributing factor, although I has been suggested that this may be a surrogate marker for low tumour or anastomotic complication which are known risk factors, rather than a results of the prolonged presence of the stoma directly (32).

Treatment of LARS

The treatment of LARS is generally approached empirically, and patients are managed according to their symptoms in a stepwise progressive fashion. Robust data on treatment methods for LARS are currently lacking, leaving clinicians for the most part with treatment algorithm based on small observational studies and expert opinion. Establishing pre-operative bowel function and incontinence is a standard part of the pre-operative consultation and this will give clinicians and patients an understanding of their best post-operative function (25). Patients with pre-operative incontinence should be heavily counselled to consider a permanent stoma given the severe difficulties that increase frequency and urgency in combination with incontinence will cause. There is good evidence that overall QoL for patients who undergo an APR with permanent end colostomies is similar to those with an anastomosis after a LAR outside of body image scores (33, 34). Preventative and surgical techniques to minimize LARS can include modified type of anastomosis, early avoidance or closure of ileostomy, avoidance of radiotherapy, and avoidance of radical resection but these options are not available to all patients for technical or oncologic reasons (21). All post-operative patients should be screened for LARS during routine follow up and anastomotic integrity confirmed to rule out complications like a leak or stricture which can exacerbated bowel dysfunction.

The initial management strategies for LARS are conservative, combining dietary modifications with fiber supplementation, (e.g.. psyllium to reduced incontinence and clustering, and anti-diarrheal agents, and loperamide which can reduce frequency and potentially nighttime continence by increasing sphincter resting pressure at the cost of increasing rates of constipation) (27). Serotonin receptor antagonists, such as Ramosteron, have also been used to treat irritable bowel syndrome due to their effect on modulating visceral afferent activity and decreasing

colonic motility and secretion and so may present a treatment option for patients with LARS (35-37). Pelvic floor physiotherapy is another tool that is widely use in the treatment of pelvic floor dysfunction and incontinence. It has demonstrated a reduction in incontinence and stool frequency when used for the treatment of LARS (21, 27). The specifics modalities of this treatment vary but can include pelvic floor muscle training, biofeedback and rectal balloon training. However, access to specialized physiotherapists as well as the associated cost can greatly hinder the implementation of this treatment.

The next treatment options for LARS on the step-wise algorithms are progressively more invasive in nature, and include transanal irrigation (TAI) and sacral nerve modulation (21), before the final treatment option, creation of an end colostomy. Transnal or retrograde colonic irrigation was proposed as a treatment for LARS in the literature as early as 1989 (38). This treatment involves the introduction of a large volume of liquid, usually water, into the colon to irrigate out the colonic contents in a controlled manner and empty the bowels. This helps reduce the symptoms of LARS throughout the remainder of the day or longer, thus giving relief to patients from the unpredictable onset of symptoms. TAI is not a curative intent treatment but rather a management strategy, as it is not likely to change neorectum physiology that resulted in the symptoms. The single irrigation in the morning or every second morning is designed to allow patients more control over their bowel movements, reduce their dependency on immediate access to the toilet and decrease severity the impact of LARS on their daily lives. TAI has since been the subject of a number of small trials for the treatment of LARS and is the treatment modality under investigation in this thesis (38-45).

The only other minimally invasive treatment is sacral neuromodulation involves the surgical implantation of a pacemaker device with electrodes extending into the sacral nerve roots. It has been used for the management of fecal incontinence from a number of difference etiologies. Its use for LARS has been investigated in small non-randomized trials with some clinical improvement (46). Percutaneous tibial nerve stimulation has been investigated as a less invasive, non-surgical option but has not demonstrated any significant benefit for patients (27).

Finally, where none of the aforementioned conservative and minimally invasive treatments attain reasonable bowel function, a permanent end colostomy is considered. This is considered by many clinicians and patients a last resort treatment as it comes with the risks an

abdominal surgery and the long-term term risk of colostomies, such as parastomal prolapse and hernia formation. Nonetheless, it allows patients some measure of control over their bowel movements and may be preferable to severe debilitating LARS. Given the many myths of living with a colostomy and underappreciation of LARS, it is important that patients are able to discuss their options with knowledgeable health care providers. Involving an enterostomal therapist early in the treatment course, as well as peer support mentors, can be invaluable in helping patients understand their option and explore management strategies.

Hypothesis and objectives:

Together the increasing incidence of rectal cancer, particularly in younger Canadians, and the advances in treatments resulting in improved overall survival have led to an expanding population of rectal cancer survivors who will have to live with the long-term sequalae of their treatments, particularly LARS. TAI represents an important management option to help patient preserve their QoL, existing between the conservative measures which are limited in their ability to control a patient's symptoms, and the surgical method that offers only a permanent stoma as a definitive solution.

Given the important role that TAI has been purposed to play in the treatment algorisms for LARS it is essential there is a systematic approach to investigating the current evidence available for this treatment, which is lacking in the current literature. This prompted the completion of a systematic review, chapter 1 of this thesis, which demonstrated that current evidence is limited in design, quality, and sample size. This treatment is not without its downsides as it requires a commitment of time, financial resources in purchasing the device and catheters, and has common minor side effects along with a very small but serious risk of serious complications. Patients need to be counselled on their reasonable expected outcomes with the treatment, both in expect impact on bowel function and on their QoL. The current evidence does not provide clinicians with the evidence base needs to widely recommend this treatment, despite recent published guidelines (21).

In this light, chapter 2 presents the protocol for an online, nurse-led, North American cross-over RCT designed to provide the high-quality evidence that is currently lacking. We aim to demonstrate the feasibility and acceptance of the TAI to Canadians living with persistent LARS despite conservative treatment. We hypothesize that TAI taught remotely and supported

through online an online portal dedicated to LARS, will positively impact the QoL and improve the symptoms of LARS of patient who experience significant dysfunction following rectal cancer surgery.

4 A systematic review of the impact of Transanal Irrigation on the symptoms of bowel dysfunction following rectal resections in adults.

A systematic review of the impact of transanal irrigation on the symptoms of bowel dysfunction following rectal resections in adults

Authors:

Jessica Holland, MD, Department of Surgery, McGill University, Montreal, Quebec, Jessica.holland@mail.mcgill.ca
Natasha Caminsky, MD, Department of Surgery, McGill University, Montreal Quebec, natasha.caminsky@mail.mcgill.ca
Carol-Ann Vasilevsky, MD, Department of Surgery, McGill University, Montreal, Quebec, carol-ann.vasilevsky@mcgill.ca
Nancy Morin, MD, Department of Surgery, McGill University, Montreal, Quebec, nancy.morin@mcgill.ca
Allison J. Pang, MSc, MD, Department of Surgery, McGill University, Montreal, Quebec, allison.pang@mcgill.ca
Marylise Boutros, MD, Department of Surgery, McGill University, Montreal, Quebec, marylise.boutros@mcgill.ca

Corresponding Author:
Marylise Boutros MD, FRCSC, FACS
Associate Professor of Surgery, McGill University
Colorectal Surgeon, Division of Colon and Rectal Surgery, Jewish General Hospital
Program Director Colorectal Surgery Fellowship Program
3755 Cote Ste Catherine, Room G-308, Montreal, QC, H3T 1E2
Phone: 514-340-8222 ext. 22773, Fax: 514-340-7560
E-mail: marylise.boutros@mcgill.ca
Twitter handle: @BoutrosMarylise

All authors contributed to the design of the study. JH, NC, and MB participated in data acquisition. JH, NC, CAV, NM, AP, MB participated in data analysis and interpretation. JH and MB prepared the first draft of the manuscript. All authors contributed to, and approved, the final version of the manuscript.

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Abstract:

Background: Transanal irrigation (TAI) can be used as a treatment for bowel dysfunction resulting from rectal surgery, known as low anterior resection syndrome (LARS). This review summarizes the current evidence for the use of TAI for bowel symptoms after rectal cancer surgery and its impact on quality of life (QoL) in adults with LARS.

Methods: This systematic review was performed as per cochrane best practice guidelines, reported according to PRISMA guidelines, and was pre-registered on PROSPERO. The MEDLINE®, Embase®, CENTRAL and web of science core databases were searched without restriction on geography, language, or date for relevant studies. A supplemental search was performed of grey-literature and national trial registries. Studies were included if adult participants had undergone surgical rectal resection with restoration of intestinal continuity, used TAI to manage the resulting LARS, and included a measure of bowel dysfunction before and after treatment. Secondary outcomes of interest included QoL, complications and patient satisfaction with TAI. Case reports or case series of less than 10 participants were excluded. Quality Assessment of included studies were done using the Cochrane's ROBBINS-I and RoB 2.0 risk of bias tool. Results were presented qualitatively as various outcome measures were used, with no predominant measure used across the different studies, thus meta-analysis was not possible.

Results: We identified nine relevant studies and three relevant abstracts. These included three case series, one cross-sectional study, four cohort studies and one randomized controlled trial. There was a total of 290 participants, with a median of 18 participants per study. The majority of participants underwent resection for rectal cancer. Bowel function was measured using a variety of scoring systems, the most common was the LARS score. The six trials which used the LARS score reported a significant benefit with TAI. Two different QoL measures were used in the minority of studies which reported on QoL and were inconsistent on the benefit of TAI. Mild side effects including abdominal discomfort, bleeding and leakage were common in some studies and not seen in others. Major complications were only reported in one study that combined TAI for LARS and other indications. All studies were at serious or high risk of bias.

Discussion: The available studies suggest that TAI may improve the symptoms of bowel dysfunction and improve the QoL of participants with LARS but are limited by design and small sample size. All the included studies were at risk of serious bias. Further high-quality research is needed using a common reproducible outcome measure and should include specific QoL measures.

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Introduction:

While advances in surgical technique and neoadjuvant treatment have increasingly allowed the restoration of bowel continuity following rectal cancer resection, they have also resulted in a significant degree of post-operative bowel dysfunction. This dysfunction, termed low anterior resection syndrome (LARS), is characterized by a constellation of bowel symptoms, including variable and unpredictable bowel habits, increased frequency and clustering of bowel movements, urgency, incontinence to gas and stool, and painful evacuation. New consensus definitions on LARS have also attempted to include the consequences of these symptoms on a patient's life, as this syndrome has a dramatic impact of the quality of life (QoL) of patients following sphincter-preserving rectal surgeries. These symptoms can have a profound impact on a patient's ability to return to work and their functional capacity which can result in long-term disability (1-3). As the incidence of rectal cancer is increasing in younger patients, LARS has been increasingly recognized as a major barrier to the functional recovery of rectal cancer survivors.

While LARS is a well recognized condition, the treatment options remain limited. Treatment algorithms, mostly based on small studies and expert opinion, follow a step wise approach starting with pre-operative counselling, then moving through a series of increasingly invasive treatments to manage the symptoms finally culminating in the creation of a permanent stoma, in the rare minority who do cannot manage their LARS symptoms (4). Accordingly, management starts in the pre-operative clinic where clinicians are encouraged to investigate the patient's current bowel function and baseline risk of LARS and counsel patients on their expected post-operative function. Following surgery, patients are counseled on managing their systems with dietary modifications, medications such as anti-diarrheal and bulking agents, and pelvic floor physiotherapy to strengthen the surrounding musculature. Unfortunately, significant uncontrolled symptoms may persist despite these measures, which require progressively more invasive treatment options.

Transanal Irrigation (TAI) is a promising non-surgical intervention to manage LARS symptoms, which can be use before progressing to surgical interventions. TAI allows patients to empty the colon in a controlled deliberate manner order to avoid the unpredictably and repetitive bowel symptoms common in LARS. It was initially developed for patients with fecal incontinence and severe constipation, but there have been small studies on its use in LARS (5).

Many of these studies are limited by a small number of patients and report heterogenous outcomes. TAI requires the use of specialized equipment and instructions, as such, this presents a significant investment of time and financial commitments on the part of patients and their health care providers. Adverse events are very rare but can be serious including rectal perforation (6).

The evidence for the use of TAI in LARS has not been systematically reviewed to date, and this comprehensive examination of the evidence for the practice is warranted before incorporating the practice into LARS management guidelines. This systematic review aimed to synthesize the current evidence for the use of TAI in the management of bowel dysfunction in adults who have undergone rectal resection.

Methods and Materials:

Study Design

We conducted a systematic review according to the Cochrane guidelines and reported it here according to the Preferred Reporting Items for systematic reviews and meta-analysis protocols (PRISMA-P) reporting guidelines (7). This study protocol was prospectively registered in the PROSPERO database of systematic reviews (PROSPERO 2021 CRD42021291094).

Literature Search Strategy:

We performed a systematic search of multiple databases for relevant literature, including Ovid Medline (1946 to present), Embase (1947 to present), Cochrane Central Registration of controlled trials (CENTRAL), and web of science core collection (1900 to present) without limits on geography, language, or date, between November 11 to 14, 2021. The first 200 results of Google scholar and the references of any identified review articles were also hand searched. Unpublished and grey literature searches were conducted on the US and European union trial registries (www.clinicaltrails.gov and www.clinicaltrialsregister.eu), Health Management Information Consortium (HMIC) Database (https://www.kingsfund.org.uk/consultancy-support/library-services), and GreyNet (OpenGrey - EASY (knaw.nl). The search strategies used are available in the supplemental materials (*Supplemental appendix 1*). We attempted to contact all authors of relevant abstracts without full text publications for further unpublished data.

Study Selection:

All study designs were included, except for single case reports and case series with less than 10 participants. Studies were included if they had participants who were adults (≥ 18 years old), with a history of rectal resection (mesorectal excision), either partial or total, with restoration of intestinal continuity, for any indication. Studies with participants with a stoma in place were excluded. Since our intervention of interest was TAI, only studies using retrograde colonic irrigation were included. Anterograde irrigation was excluded, as this treatment requires the creation of a stoma or alternative proximal access point for the irrigation and cannot be done transanally. No device limitations were placed.

Outcomes:

The principal outcome of interest in this review was the difference in bowel function before and after commencing the irrigation treatment. Bowel function could be measured by any reliable scoring system, including the number of bowel movements per day, the number of nocturnal bowel movements, the LARS score, or one of the other commonly used bowel function scoring systems, such as the Memorial Sloan Kettering Bowel Function instrument (MSKCC BFI) scale, Wexner/Cleveland Clinic Fecal Incontinence Score (CCFIS), St. Mark's (Vaizey) Incontinence score or Altomare Obstructed Defaecation Syndrome (ODS) score.

Secondary outcomes of interest included: change in QoL, as measured by any standardized QoL scoring system before and after TAI, rate of complications of TAI, patient satisfaction with bowel function and with the treatment, the rate of treatment failure (as reported by the proportion of participants who were offered the treatment and declined to participate, proportion of participants who discontinued treatment within the period of study due to intolerance, and proportion of participants during the trial who required an ostomy creation for uncontrolled symptoms).

Study selection methods:

All references identified were saved in an EndNote reference manager. Duplicated results were subsequently removed in the automated process and confirmed through manual review. Initial title and abstract screening were then performed by two separate investigators (JH, NC) independently for inclusion. All publications identified as relevant by either reviewer were marked for full review. No articles selected for full text were excluded on the basis of language

of publication and translation was planned if needed. Full text review was then performed by both reviewers independently and the reasons for exclusion at this stage were reported. Any disagreement on inclusion or exclusion was resolved by consensus without need for a third-party arbitration.

Data extraction and reporting methods:

Two independent reviewers (JH, NC) performed individual data extraction into a standardized form. Disputes were resolved by consensus discussion, and where necessary, arbitration by a third reviewer (MB). Where available, the change in median score of bowel dysfunction was recorded. Various scoring systems for bowel dysfunction were used in the individual studies and there was no one common effect measure used amongst the studies, thus a descriptive summary of the reported scores is given in Table 3. It was not possible to report a single pooled effect measure, and results were therefore reported qualitatively. A data synthesis and meta-analysis was considered but was not possible given this limitation regarding a common effect measure. Furthermore, significant heterogeneity in the study population would have made a meta-analysis inappropriate. There was limited data available on the level of individual patients, so planned subgroup analysis stratification on the basis of LARS score or history of radiation was not performed. Likewise, the limited number of studies prevented subgroup analyses by study type and assessment of publication bias.

Quality assessment methods:

Quality assessment of included cohort and cross-sectional studies was performed using Cochrane's ROBINS-I assessment tool for non-randomized studies and the RoB 2.0 Revised risk-of-bias tool for randomized controlled trials (8, 9). This was done independently by each reviewer, and the consensus results reported. The resulting figures for this data were generated using the freely available *robvis* software tool (10).

Results:

Search Result:

The systematic searches identified 1829 records. After removing 542 duplicate records, 1287 underwent primary screening by title and abstract (Figure 1). Ninety-four records

underwent further full text review, with abstracts included whenever available data indicated a relevant study. Ultimately, 12 studies in total were included: 9 full text publications (11-20) and 3 abstracts (21-23). Two of three abstract authors responded to our attempts to contact them (21, 22), and one was able to provide further data (21). None of these three studies are currently published to our knowledge. From the US National Library of Medicine Clinical Trials Registry, there appear to be four relevant ongoing trials registered, including one by our own group, and one trial completed in July 2016 (NCT04246775). The completed trial, from the United Kingdom, does not appear to be published to date and no contact information for the authors was available.

Study Characteristics

Of the included 12 published studies, there were three case series, one cross-sectional study, four cohort studies and one randomized control trial (Table 1). In total, 290 patients met all inclusion criteria and were included, with a median of 18 patients per study. Three potentially relevant studies were eventually excluded due to their reporting structure which limited our ability to determine the effects of TAI on participants' bowel function with a consistent subjective or objective measure (12, 24, 25) however they do contain interesting results that we felt warranted mention in this report and are detailed below under late excluded studies.

Late Excluded studies

McCutchan *et al* published a qualitative study consisting of semi-structured interviews with 17 patients who were offered TAI: 12 participated in the intervention and 5 who declined functioning as a comparator arm (12). No objective or consistent measure of pre and post bowel function was measured, thus the study was excluded from this review. In this study, the authors reported that patients who declined the treatment felt that they had less severe or improving symptoms and were concerned about the technical ability and 'distressing' nature of TAI. Patients who accepted the treatment had more severe LARS symptoms, were unable to control their current symptoms, and were willing to 'try anything'. Participants who completed the treatment described its impact as 'life changing'.

Harji *et al*. presented a pilot feasibility study of a stepwise treatment program for bowel dysfunction following rectal cancer surgery, the BOREAL program (25). This study included

137 patients who underwent rectal resection for cancer between 2017 and 2019 and focused on early treatment of LARS in the first 12 months after surgery. At 3 months, patients with uncontrolled symptoms were offered TAI, pelvic floor physiotherapy and biofeedback. Treatment effects were measured by CCFIS, LARS score and EuroQol (EQ)-5D questionnaires. There were 12 patients treated with TAI during the trial, but the success of TAI on its own, as an intervention, was not reported. This study was notable for the systematic assessment of patients' symptoms and providing a concrete treatment algorithm which could be followed clinically.

Only two RCTs were identified in this search; one was included in this review (20, 24). The second, Rosen *et al* 2020, used TAI to prophylactically manage symptoms immediately after surgery, as opposed to a treatment for established LARS (24). As a result, the trial did not have any pre-treatment measure of bowel function and was unable to provide a measure of change in bowel function with TAI. The authors reported significantly better LARS scores and number of bowel movements per day at 3 months for participants using TAI compared to those that were not using the treatment, but no superiority in QoL, as measured by the SF-36 mental and physical components, for the TAI group (26). A follow up study was published with the results at 12 months, reporting that 9 of the original 18 TAI patients still performed the irrigations and one patient out of 19 from the standard of care arm had crossed over to the TAI arm (24). The authors did not observe a significant difference in QoL at this time-point either.

<u>Abstract only studies</u>

Limited data was available from the three studies in abstract form. Zucchi *et al*. presents the largest published cohort of 80 patients with LARS treated with TAI, in a multicenter Italian study. The authors reported a significant improvement in patients' LARS scores with the use of TAI from 33.7 $\pm$10.4 pre-treatment to 0.5 $\pm$3.1 at 24 months (23). However, further data on this study are unavailable, and we were unable to reach the authors for further details. Faulkner *et al*. presented a smaller retrospective group of 13 patients, reporting that 9 of these patients were satisfied with the TAI treatment (22). The authors responded with the details included in Tables 1-3. Similar to Harji *et al*, Sargenti *et al*. reported an attempt to create a standardized stepwise program to provide care to patients with significant LARS following rectal resection (21). Participants were screened by their clinical team, and their symptoms were assessed at 30, 60 and 180 days. Participants were initially treated with colonic irrigation, and then offered

posterior nerve stimulation and volumetric rehabilitation if their symptoms did not improve. The study reported improved LARS scores for participating patients, from a mean of 28 to 25 with TAI. Only 5 patients were satisfied with TAI, and the remaining 13 went on to further treatments.

Characteristics of patients in included studies

In total 290 patients met inclusion criteria and had partially extractable data. Participant characteristics are reported for the included studies in Table 2. Most of the participants were aged 50-70 years and underwent anterior resections (AR) or low anterior resections (LAR), although the studies did also include some patients who underwent subtotal and total colectomies. Not all studies reported the indication for resection but in those that did, the majority were performed for rectal cancer. The majority of anastomoses were stapled, although handsewn anastomoses were also common. Four of the trials report primarily on chronic LARS, at least 6 months after surgery or ileostomy reversal (13, 14, 16, 20). Two trials reported on early LARS (15, 19), and the remaining five trials did not differentiate (11, 17, 18, 22, 23). The majority of these studies were conducted in Western European countries, with two studies from Japan and Brazil (11, 14).

Characteristics for the Transanal Irrigation (TAI) treatments:

TAI was primarily taught during an in-person visit with a nurse at a specialized center or clinic. Participants who became comfortable enough to perform the irrigations would then perform them independently at home. The two irrigation devices most commonly used were a rectal balloon system (Peristeen®) and a cone irrigation system (Braun®). Only one trial used the colostomy irrigation kit, and this was a deliberate choice in an attempt to reduce the cost of the irrigations to make it economically feasible to offer it to a wider population (14). The irrigation patterns and volumes were variable between trials and between individual participants. The initial volume was often around 1000 ml of water, then increased or reduced by participants as they tailored TAI to their individual needs and tolerance. The irrigation was often started on a daily pattern, and then patients were allowed to reduce the frequency as needed, down to as infrequently as weekly. Daily irrigations to one irrigation every second day remained the most common pattern. The time required for the irrigations was inconsistently reported, however,

Rodrigues *et al* reported that all participants were able to complete the process in less than one hour by 12 months and Koch *et al* reported a mean irrigation time of 43.9 min ±27.3min (14, 16). (Table 2)

Assessment of Outcomes:

Primary Outcome: Change in Bowel Dysfunction

The LARS score was the most common objective measure of bowel dysfunction reported, but trials also used a variety of other scoring systems such as: the CCFIS, Williams' incontinence score, Vaizey, and Altomare ODS score, MSKCC BRI score and the number of bowel movements per day. Where reported, all studies consistently demonstrated a reduction in LARS scores with TAI (14, 15, 19-21, 23). Similarly, all other objective measures reported a significant reduction in the individual scores of the system chosen, except one study which used the Altomare score and did not report a significant improvement (13, 16, 19, 20). When using loosely defined terms such as satisfaction, return to reasonable bowel function, success or effective symptom control, the results were more variable. Faulkner *et al* reported 70% satisfaction with treatment, Iwama *et al* 100% success at 'reasonable' bowel function, Gosselink *et al* 79% participants achieved 'effective' control and Christensen *et al* reported only 40% had success with treatment (11, 17, 18, 22). (Table 3)

Secondary Outcomes:

Four studies attempted to determine the effect of TAI on QoL through established scoring methods. The SF-36 was used in three studies. Rosen *et al* demonstrated an improvement in the SF-36 mental health domain, 46 (53-55) to 55 (45-60), and no significant improvement in the physical domain, 55 (41-60) to 56 (49-62). Martellucci *et al* saw significant improvements in the mental health (38 to 53), social functioning (43 to 49), emotional role function (39 to 47), bodily pain (39 to 47), but not vitality (47 to 53), physical function (55 to 57), or general health perception (42 to 53). Rodrigues *et al* reported improvement in all domains, but these changes were significant only in vitality (mean 52.5 to 75.0, p-value 0.025), physical (mean 25.0 to 100.0, p-value 0.002), social (mean 43.8 to 87.5, p-value 0.001) and emotional domains (mean 16.7 to 100, p-value 0.001). Alternative QoL measures including the American Society of

Colorectal Surgery bowel QoL and the EORTIC-QLQ-30 were both used in one study each demonstrating an overall improvement in scores (13, 20).

Treatment acceptability by patients in these studies could be defined by the number of patients who were offered TAI and accepted the intervention. Rodrigues *et al* offered 35 patients with persistent LARS after 6-12 months of conservative treatment, 22 (63%) patients agreed to participate. Martellucci *et al* offered TAI to patients with major LARS only (LARS score > 30) and only 1 of 33 patients declined. In a less select cohort including a variety of defecatory disorders, Gosselink *et al* reported 89% of patients who were offered TAI chose to start the irrigations. In the only RCT in this review, of 13 patients randomized to irrigation, only 10 (77%) accepted the treatment and 3 withdrew once randomized to TAI (23%).

Many trials reported the number of participants who discontinued TAI during the period of the trial and the reason for the discontinuation varied widely between studies. Faulkner reported a 30% (4/13) discontinuation rate due to cancer recurrence, difficulty with use and symptom resolution. Sargenti *et al* reported a 72% (13/18) dissatisfaction rate with treatments by 6 months and these participants went on other treatments. Zucchi reported a 20% discontinuation rate, but the reasons were not given in the abstract. Iwama *et al* reported that 20% (2/10) continued use of TAI at 5 years due to symptom persistence but reported that the remaining patients had achieved 'reasonable' bowel function without further treatment. Rosen *et al* reported a 35% (5/14) discontinuation rate temporarily but all restarted the treatment as the symptoms returned. Koch *et al* reported a 19% (5/26) cessation rate; one patient stopped TAI due to improved symptoms and the other four discontinued due to dissatisfaction with treatment, one of whom went on to the creation of an end stoma. Gosselink *et al* reported that less than 20% of the participants who used TAI to manage the symptoms of LARS discontinued the treatment over 80 months. In the Martellucci *et al* cohort, 15% (5) of patients discontinued the treatment, 3 for cancer recurrence, 1 for proctitis and 1 for general dissatisfaction.

<u>Complications, Side Effects and Safety</u>:

Complication rates and side effects of treatment were reported in the majority of trials, with variable rates observed. Some studies reported mild but relatively common side effects with TAI in 24-75% of participants (13, 17, 18). These side-effects included: transient abdominal pain, minor rectal bleeding, anal pain, technical problems, and loss of irrigation fluid. A few

studies reported no complications or side effects with treatment in any participants (11, 14, 19). Only one study reported serious complications with the irrigations (18). This retrospective review of 348 patients using TAI for any indication (only 15 for LARS) in a single center in Denmark reported two perforations caused by the irrigations, both required surgery. One patient was performing irrigations for major fecal incontinence and constipation, and the indication for the other patient was not reported.

Assessment of Quality and Bias:

Quality assessment using the ROBINS-I tool was performed for the cohort and cross-sectional studies. All included studies had serious risk of bias identified (Figure 2). The RoB 2.0 tool was used for the single included RCT and identified concerns with the trial design, placing the trial at high risk of bias (Figure 3).

Discussion:

This systematic review presents a summary of the current evidence on the use of TAI for the management of bowel dysfunction after rectal cancer surgery. It included nine full text studies, only one of which was a RCT. Overall, there were significant concerns in regard to the quality of the studies included, and as a result the current evidence for TAI as a treatment for LARS remains limited. While the available data, albeit sparse, suggests that TAI may significantly improve symptoms in specific patients, it is unclear which patients could benefit most from TAI, and whether or not the improvement in bowel function demonstrated will translate into a sufficiently improved QoL to justify the resource and time investment that TAI requires by both the patient and their clinical team.

A significant issue that our systematic review uncovered was the lack of standardized measurement of bowel function across the included studies, with 8 different scores being used. The LARS score was the most frequently used, 5/12 studies, and most common in recent studies. Despite the fact that this score has limitations, the simplicity of its use has made it relatively easy to introduce into clinical practice and research studies (27). A reduction in overall LARS score has been correlated with an increase in QoL in other observational trials, so the improvements in LARS score seen Zucchi *et al*, Dalsgaard *et al*, Martellucci *et al*, Rodrigues *et al* and Enriquez-

Navascues *et al* are encouraging support for the treatment (27). It is a reasonable surrogate marker to include in further trials, but an effort should be made to also include more direct measures of QoL using measures like the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core Module (EORTC QLQC30) used by Enriquez-Navascues *et al* (28).

Most trials only managed to include a small number of participants, likely due to a combination of the invasive nature of TAI and the select patient population motivated to try the treatment. In their qualitative study, McCutchan *et al* reported that anxiety about performing the irrigations was universal prior to starting treatment (12). Patients who felt that their symptoms were manageable or improving, despite having a LARS score over 20, declined the treatment. The number of patients who accepted TAI varied widely between trials from 63% to 97% despite all participants offered TAI having been identified by their clinical team as potentially benefiting from the treatment (14, 19). The largest cohort reported achieved their sample size by recruiting patients from multiple centers (23). Despite the remaining trials being conducted at large centers with referrals specifically for LARS and being conducted over several years, it seems that a limited number of patients were generally deemed suitable or were willing to participate in these trials. A cooperative approach between colorectal centers will be required to obtain sufficient number of patients to achieve statistical and clinical relevance in future trials.

Identifying the ideal patients who would benefit most from TAI is difficult given the heterogeneous nature of the patients included in these studies. The two most straightforward ways to clinically differentiate patients who may benefit would be on the basis of the time since their operation, specifically early and late LARS, or on the severity of their symptoms, as no, minor, or major LARS as per their LARS score. Patients with early LARS, in the first six months to a year after surgery, are likely to see natural improvement of LARS symptoms with time given our understanding of the nature of LARS and are less likely to have adequately tried the conservative measures suggested for management (29). Allowing this time to pass also allows for any anastomotic issues to be identified before any potential repetitive traumatization of the area occurs during TAI. Patients with more severe LARS are naturally more inclined to seek treatment and would likely see the greatest improvement in their QoL as it has been the most

severely impacted by their symptoms. Unfortunately, these current evidence does not allow us to identify a specific target population of LARS patients for TAI treatment.

Patients with early LARS are often at the peak of their symptoms and can be identified in their routine cancer follow up at 3 and 6 months as suggested in the studies by Dalsgaard *et al*, Sargenti *et al*, and Martellucci *et al* (15, 19, 21). These patients were offered TAI to manage their early LARS with variable success. Sargent *et al* found that only 5 of the 18 patients (28%) included with significant LARS were satisfied with the treatment and the other 13 went onto other options (21). Dalsgaard *et al* had 17 patients treated with TAI out of 86 with bowel dysfunction identified in their initial screen, all at least 3 months out from their surgery (15). Unfortunately, while they report a reduction in LARS score for 10 patients, the long-term success of the treatment was not reported. Martellucci *et al* offered treatment to patients with both early and late LARS, but the individual breakdowns of effectiveness for both groups was not available (19). We have no evidence to date that TAI intrinsically changes the function of the new rectal reservoir. A recent paper by Rosen et al. investigated the potential for TAI to be used in a prophylactic manner to treat LARS. The authors observed an improvement in CCFIS at 3 months, but at 12 months there was no significant improvement in bowel function and many participants had stopped treatment (24, 26). Taken together, all available studies suggest that symptoms return after discontinuation of TAI (19). Early TAI may improve the first year of living with LARS but it may also increase the stress on patients in this difficult period whose symptoms would improve without TAI and could discourage patients from trying this treatment later if their experience in these first months was negative.

Late LARS symptoms are more established, and many patients have exhausted the conservative measures by this point. Rosen *et al*, Rodrigues *et al*, and Enriquez-Navascues *et al* specifically identified patient who had insufficient improvement with at least 6 to 12 months of conservative management before entering their trials. In two trials, Rodrigues *et al* and Enriquez-Navascues e*t al*, 30% and 37% of patients respectively offered TAI still declined. These three trials also demonstrate improvement in the specific bowel function and QoL questionnaires for the patients who did participate. Only one patient across these three trials discontinued TAI permanently after starting; 5 discontinued treatments temporarily but restarted TAI once the symptoms returned. Similarly, the cross-sectional study by Koch *et al* consisted of participants

with primarily late LARS, a mean of 3.1 years since their operation, and of the 26 patients included, only four discontinued TAI due to dissatisfaction with the treatment. Despite 62% reporting minor sided effects, 81% of patient were still using the treatment at a mean of 19.2 months (3, 12). In these studies, it seems that patients' decision to try TAI may be a larger hurdle than having patients continuing the treatment if their LARS remains significant after conservative measures have been exhausted.

Patients could also be selected for TAI on the basis of symptom severity. Major LARS has the strongest correlation with a reduction in QoL in a number of studies, but there are some concerns with this approach as it may exclude patients with lower LARS scores whose symptoms dramatically impact their life (30, 31). Martellucci *et al* demonstrated a much higher (97%; 32/33) acceptance of TAI than the other trials. They offered therapy to both early and late LARS participants but only to patients with major LARS (LARS score > 30). They had a slightly higher rate of treatment discontinuation (5/32, 16%) than the studies focusing on late LARS alone. All but one of the studies in this review who included a LARS score for their participants, included had an initial mean or median score in the major LARS range suggesting that this may have been an unstated selection criteria by either the clinical team or a minimal symptom level before patients would be likely to agree to participate (21). As the LARS score was initially designed as a screening tool, using this to screen for patients who might benefit from TAI may be a good use of this clinical tool.

The wide variation in reported rates of side effects and complications is difficult to interpret. It seems counter-intuitive to have some studies reporting mild side effects at a rate of 63% to 75%, while others reporting no side effects at all with similar sample sizes (14, 16, 17, 19). It may very well come down to individual study reporting of side effects, nonetheless, severe complications like perforation are rare, reported in only one study, comparable with the other published risk rates (6, 18).

Conclusion

In this review, we have demonstrated that there is some evidence for the use of TAI to manage bowel dysfunction after rectal surgery, and while it may be reasonable to be introduced to clinical practice as part of a systematic step wise approach to the management of LARS, there are currently major gaps in the evidence supporting its us. For some patients, the treatment is

'life-changing', while for others they may spend close to an hour in the bathroom each morning on a treatment without any significant improvement in their QoL. These studies have highlighted that there is a need for a reliable universal measure to assess the impact of LARS treatment strategies on bowel dysfunction, and future studies should include a direct measure of participants' QoL, to ensure improving bowel dysfunction using TAI truly improves patient QoL. At present, the evidence does not support any clear patient selection criteria for TAI. Further high-quality research is needed on the use of TAI for LARS before its widespread adoption into clinical guidelines.

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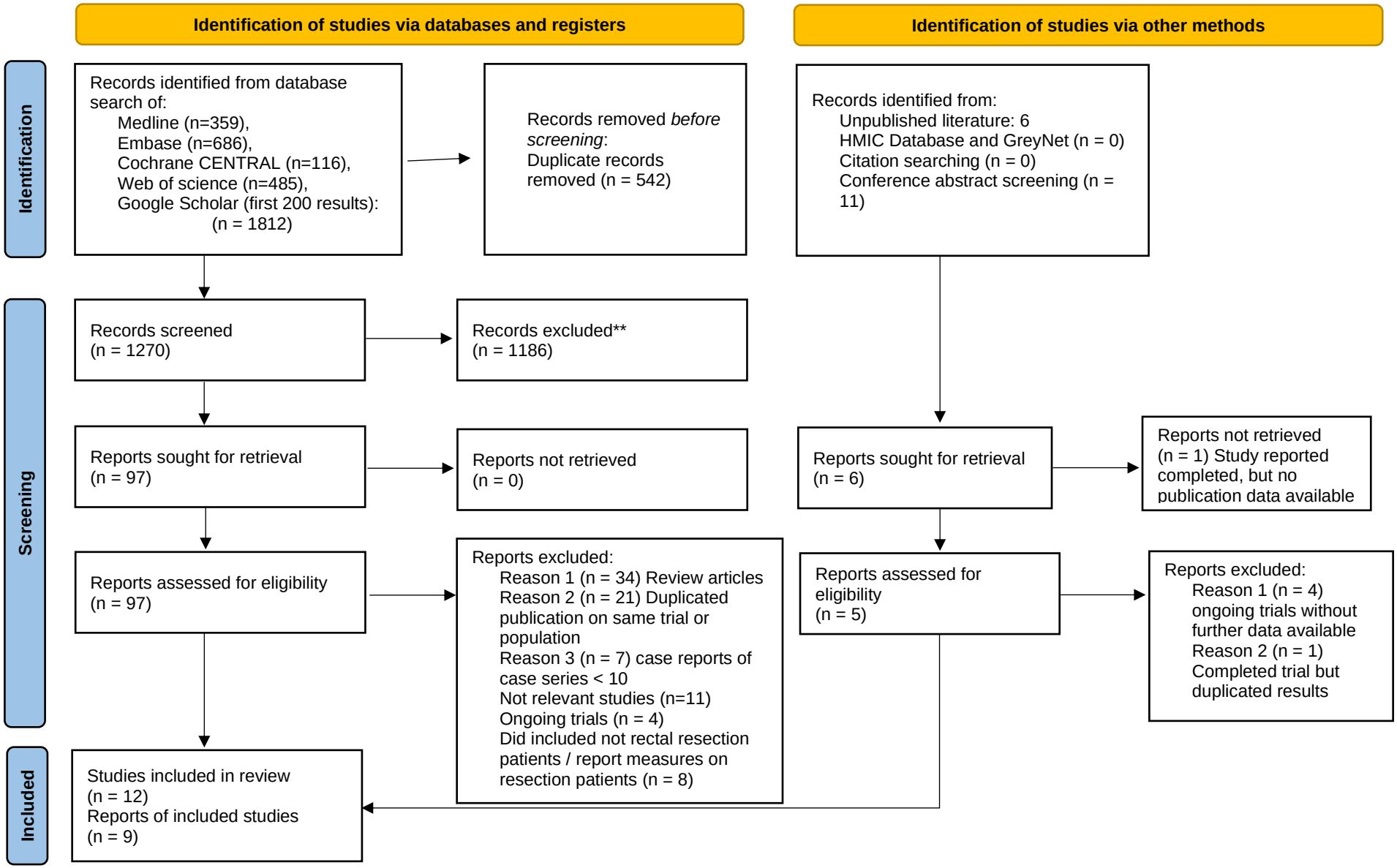

Figure 1 Flow Diagram of Study Selection, adapted from PRISMA 2020 Flow Diagram

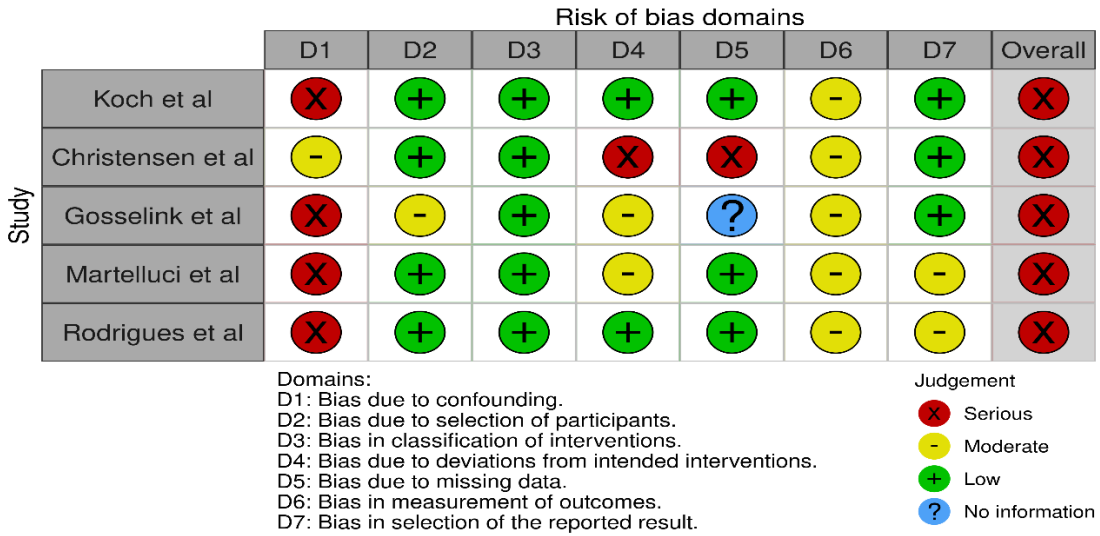

Figure 2 Cochrane's ROBINS-I Quality assesment cross-sectional and cohort studies

Figure generated using the *robvis* tool (47)

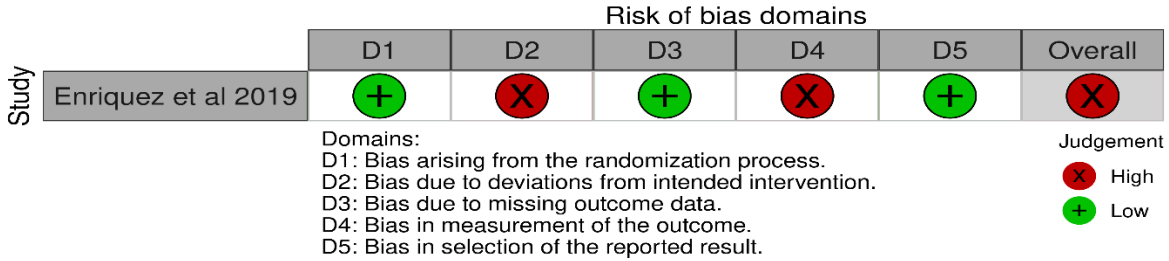

Figure 3 Cochrane's RoB 2.0 Quality assesment of randomized controlled trials

Figure generated using the *robvis* tool (47)

Table 1: Study Characteristics

Publications	Georgraphical location	Date of study	Relavant patients (TAI / Total)	Follow up Duration (months)	Primary outcomes reported	Secondary outcomes reported
Abstract only						
Faulkner *et al*. 2014	Manchester, UK	2007 – 2013	13	1-39 (range)	# BM/day, Satisifacation with tx	DC tx
Sargenti *et al* 2019	Pisa, Italy	2014 – 2019	18 / 41	4.7 (median)	LARS score	DC Tx
Zucchi *et al*. 2019	Multicenter, Italy	2016 - 2018	80	24	LARS score	VAS QoL, DC Tx
Case series						
Iwama *et al*. 1989	Japan	NR	10	'several'	Reasonable bowel function	Ongoing use after trial
Rosen *et al*. 2011	Vienna, Austria	2006 - 2009	14	Median, range 29 (15, 46)	# BM/day, # BM/night, Cleveland Incontinence score	SF-36, ASCRS Questionnaire, complications, DC Tx
Dalsgaard *et al*. 2020	Aarhus, Denmark	2012 - 2016	17 / 190	Median IQR 6 (3, 12)	LARS Score	NR
Cross-sectional						
Koch *et al*. 2009	Masstricht, Netherlands	2008	26	Mean, SD: 19.2 (± 13.2)	William's incontinence scores	Complications, Stoma, DC Tx
Cohort						
Gosselink *et al*. 2005 Retrospective	Rotterdam, Netherlands	1989 - 2001	29 / 190	Median, range: 56 (8, 154)[1]	"effective control" of symptoms	Patient satisfication with TAI
Christensen et *al*. 2009 Retrospective	Aarhus, Denmark	1994 - 2004	15 / 348	Mean, range: 21 (1, 116)[1]	'successful treatment'	Usage pattern
Martellucci et *al*. 2021 Prospective	Florence, Italy	2015 - 2016	33	6	LARS score, # BM/day, Night BM, MSKCC BFI scale	SF-36, VAS, DC Tx
Rodrigues *et al*. 2022 Prospective	Belo Horizonte, Brazil	2003 - 2014	22 / 35	12	LARS score Wexner Incontinence score	SF-36, complications, Declined Tx, DC Tx
Randomized control trials						
Enriquez-Navascues *et al*. 2019	San Sebastian, Spain	2017 - 2018	14 / 27	6	LARS score, Vaizey, Altomare ODS Score	SF-36, EORTC-QLQ-30, VAS, DC Tx

NR = Not reported, DC Tx = discontinue treatment, VAS QoL = Visual Analogues scale, SF-36 = 36 Item short survey, EORTC-QLQ-30 = EORTIC Quality of Life questionnaire, MSKCC BFI score = Memorial Sloan Kettering cancer center Bowel Function instruement, [1]For entire cohort

Table 2: Participant and Irrigation Characteristics

Publications	TAI patients (n.)	Sex (no. Males)	Median age (IQR)	Operative characteristics	Reason for resection	Time since operation	Irrigation Device	Irrigation volume (median, range)	Pattern of irrigation
Abstact									
Faulkner *et al*	13	8	67 (52,82)	11 LAR / 2 other	Rectal cancer	NS	NS	NS	NS
Sargenti *et al*	18	NR	66 (32, 87)	AR	NS	30 - 180 days	Cone system	NS	NS
Zucchi *et al*	80	NS	NS	NS	NS	NS	NS	NS	NS
Case series									
Iwama *et al* 1989	10	7	63.5 (58.5, 70)	AR / LAR 5 handsewn 5 stapled	Rectal cancer	NS	Cone irrigation, (Hollister or Tokyo Eizai Co.)	500 ml (200, 850)	1/day to 1/week
Rosen *et al* 2011	14	11	68 (45, 80)	AR / LAR 6 handsewn 8 stapled	Rectal cancer	≥ 9 months	Rectal balloon system (Peristeen®)	900mL (500, 1500)	1/day to 1/3days
Dalsgaard *et al*. 2020	17	NE	63 (35, 87)[?]	LAR	Rectal cancer	≥ 3 months	NR	NR	NR
Cross sectional study									
Koch *et al*. 2009	26	21	67.6 (±7.4)	Unspecified	Rectal cancer	3.1 years (mean)	Cone irrigation (Braun®) Optional balloon	1500 mL (± 210) *mean*	1/day – 2/day
Cohort studies									
Gosselink et al. 2005	29	14	53 (25, 81)[1]	18 LAR / 8 Ileoanal	NS	NS	Cone irrigation (Braun®)	1000ml (500 – 3000)	5x/day to 1Q4days (median 1/day)
Christensen *et al*. 2009	15	NE	52 (5, 85)[1]	Unspecified	NS	Unspecified	Rectal ballon system (Peristeen®) or Cone irrigation	961 ml (10-2000)[1,3] Mean and range	Unspecified "trial and error" (daily to 1/wk)[1]
Martelluci *et al* 2021	33	17	61 (29-93)	LAR / AR/ Total 3 handsewn 24 stapled	25 Cancer 1 UC 1 Diverticular	>1 month	Rectal balloon system (Peristeen®)	450ml (300 to 1000)	Q2 days
Rodrigues *et al* 2022	22	6	58.59 (± 12.02)	LAR 5 handsewn 17 stapled	Rectal cancer	≥ 6 months[3]	Colostomy irrigiation kit	Unspecifed	Daily
Randomized controlled trial									
Enriquez-Navascues *et al*. 2019	13	9	68 (48, 71)	Low AR 10 Stapled 3 Handsewn	Rectal cancer	>12 months	Rectal balloon system (Peristeen®)	1000 ml[3]	1/day to 1/2day

*NS = Not specified, NE = Not extractable as data is only available for entire cohort, LAR = Low anterior resection, AR = Anterior resection, UC = Ulcerative colitis

[1]Data for the entire cohort, unable to isolate LARS patients, [2]conflictindg 6 or 12 months in initial trial reprt , [3]Volume of water was adjust to individual's patient comfort

Table 3: Study Outcomes Measures

Publications	Patients (n.)	Primary Outcomes Effect measure	Outcomes	Secondary outcomes	Outcomes
Abstacts					
Faulkner *et al*.	13	Satisfaction with tx	9 / 13	DC tx	4
Sargenti *et al*	18	LARS (mean)	28 to 25	DC Tx	13
Zucchi *et al*	80	LARS score @ 1month @ 24months	33.7 (±10.4) 11.3 (±12.5) 0.5 (±3.1)	VAS at 1 mth DC Tx	2.3 (±1.4) to 6.8 (±2.1) 20%
Case series					
Iwama et al. 1989	10	Reasonable bowel function	100% successful	Ongoing use at end of trial	2 patients ≥ 5 years
Rosen *et al* 2011	14	# BM/day, # BM/night, Cleveland incontinence scores	8 (4-12) to 1 (1-2) 3 (2-5) to 0 (0-0) 17 (15-20) to 5 (4-9)	SF-36 Mental SF-36 Physical ASCRS QoL Complication[1] DC Tx (temp)	46 (35-55) to 55 (45-60) 55 (41-60) to 56 (49-62) Sign. improvement all domains 7 (50%) 5
Dalsgaard *et al*. 2020	17	LARS score (median, IQR)	39 (35-41) to 28 (13-36)	NR	NR
Cross sectional studies					
Koch *et al*. 2009	26	William's incontinence scores (mean)	4.4 (± 0.07) to 1.7 (± 1.7)	DC Tx Stoma Complications[1]	5 1 16 (63%)
Cohorts studies					
Gosselink et al. 2005	29	"effective control"	79% successful	DC Tx Complications[2]	< 20% at 80mths 75% (Abdominal discomfort, technical, time, loss, anal pain)
Christensen *et al*. 2009	15	Succesful treatmnt	6 (40%)	Complications[2]	24%
Martelluci *et al* 2021	33	LARS score (median, range), # BM/day, Night BM, MSKCC BFI scale	35.1(30-42) to 12.2(0-21) 7 (0-14) to 1 (0-4), NR NE Sign. improved	SF-36 Complications Decline Tx DC Tx	Sign. Improve in 4 domains 0 1 5
Rodrigues *et al* 2022	22	LARS score (median, IQR)	39 (±4) to 8 (±9)	SF-36, Complication Declined tx DC Tx	Sign. Improve in 4 domains 0 13 / 35 approached 1
Randomized controlled studies					
Enriquez-Navascues *et al*. 2019	13	LARS score (median, IQR) Vaizey Altomare ODS	35 (32-39) to 12 (12-26) 15 (11-15) to 6(4-7) 10 (7-14) to 8(6-9)	EORTC-QLQ-30, VAS DeclinedT Tx	Global score sign improved 2(0-3) to 7.5(6-9) 3

NE = Not extractable as data is only available for entire cohort [1]Complications: transient abdominal pain/cramps, minor rectal bleeding, leakage, time consumption, and others, [2]Data for the entire cohort, unable to isolate LARS patients

Supplemental Appendix.

Search strategy:

Ovid Medline Search strategy:

Ovid MEDLINE(R) ALL <1946 to November 11, 2021>

1 rectal surg*.mp. 1920
2 anterior resection*.mp. 5358
3 LARS*.mp. 4307
4 low anterior resection*.mp. 3050
5 anterior rectal resection*.mp. 298
6 sigmoid resection*.mp. 730
7 (anterior adj2 resection*).mp. 6262
8 (anterior adj3 resection*).mp. 7192
9 Proctectomy/ 1108
10 proctectom*.mp. 2414
11 Rectum/su [Surgery] 11880
12 therapeutic irrigation.mp. or exp Therapeutic Irrigation/ 52932
13 irrigation*.mp. 42850
14 washout*.mp. 27562
15 self washout*.mp. 3
16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 25357
17 12 or 13 or 14 or 15 104499
18 16 and 17 360

Embase Classic+Embase <1947 to 2021 November 12>

1 rectum resection/ or rectum surgery/ or rectum anastomosis/ 15270
2 rectal surg*.mp. 4235
3 exp rectum anterior resection/ or exp rectum resection/ 20955
4 anterior resection*.mp. 10645
5 LARS*.mp. 6435
6 exp rectum anastomosis/ or exp rectum anterior resection/ or exp rectum resection/ 21603
7 exp sigmoidectomy/ or exp colon resection/ 50212
8 (anterior adj2 resection*).mp. 11982
9 (anterior adj3 resection*).mp. 13243
10 proctectom*.mp. 2500
11 exp rectum surgery/ 29718
12 therapeutic irrigation*.mp. 75
13 irrigation*.mp. 45311
14 washout*.mp. 41322
15 self washout*.mp. 3

16 12 or 13 or 14 or 15 86308
17 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 88408
18 16 and 17 686

CENTRAL

Search Name:
Date Run: 14/11/2021 23:36:10
Comment:

ID Search Hits
#1 (rectal surg* OR anterior resection* OR LARS* OR Low anterior resection* OR anterior rectal resection OR sigmoid resection* OR proctectom* OR rectal resection):ti,ab,kw AND (transanal irrigation* OR therapeutic irrigation* OR irrigation* OR washout* OR self washout*):ti,ab,kw (Word variations have been searched) 116

Web of science

https://www.webofscience.com/wos/woscc/summary/002e9f88-5308-46bf-b1da-1f9f30a9ebc5-1307e7ba/relevance/1

Nov 14, 2021 at 630PM

Topic search: rectal surg* OR anterior resection* OR LARS* OR low anterior resection* OR sigmoid resection* OR proctectom* AND irrigation* OR washout* OR self washout* OR therapeutic irrigation

Google scholar search

(rectal surg* OR anterior resection* OR LARS* OR Low anterior resection* OR anterior rectal resection OR sigmoid resection* OR proctectom* OR rectal resection) AND (transanal irrigation* OR therapeutic irrigation* OR irrigation* OR washout* OR self washout*) 12:52PM 2021-11-18

11 results Google search
Results 436 results Google scholar search

5 Addressing the knowledge gaps on the use of Transanal Irrigation for the management of LARS

The systematic review in the proceeding chapter presents a summary of the current evidence for the use of TAI for the management of LARS. We identified three case series, one cross-sectional study, four cohort studies and one randomized control trial, which suggested a benefit of TAI for patients with LARS who have not responded sufficiently to conservative therapies. In these studies, an improvement in the various measures of bowel dysfunction and QoL was observed. Despite the potential benefits suggested, all of the studies were limited by design, sample size and a lack of standardization in the outcomes measured. There was a median of 18 patients with LARS included in each trial, the majority with major LARS, and only 290 patients with LARS treated by TAI included across all the trials. Given patient reluctance to commit to TAI management as demonstrated in some of these studies, obtaining a sufficient sample of patients to be sufficiently powered to demonstrate a true impact of the treatment will require a multi-center approach. It appears that while LARS is extremely common, patients motivated and appropriate for TAI maybe less so. The lack of a standardized shared outcome measure hampered our ability to compare results across trials and prevented any serious consideration of a meta-analysis. As a result, the evidence presented in this review is encouraging but not sufficient to include TAI in the standard treatment approach to the management of LARS at this time.

The following chapter details the protocol for a multicenter crossover RCT designed to address the limitations in the previous studies and provide high quality evidence on the effect of TAI both on bowel function and the QoL. We have designed this study to address some of the most significant gaps in the current literature, including a multicenter cross over design was chosen both to maximize the population of patients with LARS who could be recruited in the trial and minimize the sample size required by having participants function as their own controls. Given the required selection criteria, including significant LARS and motivation to pursue this intensive intervention, a traditional RCT would require screening and recruiting a large sample and may be more difficult to complete. A crossover design also allows for the most homogeneity amongst the control and treatment arms. This design also addresses the concern that LARS will change overtime by having participants track their symptoms in a reproducible bowel diary over

three months and arranging the cohorts so that participants enter the treatment arm either before or after the control arm. The unique online virtual platform for teaching TAI will increase the accessibility for participants outside the immediate geographical area of a tertiary academic colorectal center. By using a combination of LARS score, the CCFIS, and EORTIC-QLQ-C30 as well as a satisfaction questionnaire, we aim to provide reproducible patient centered outcomes which clinicians can use to counsel patients on LARS treatment with TAI. The following chapter provides a detailed protocol for the trial, which has been approved by the Ethics Committee at the Jewish General Hospital, and the RCT has started in January of 2022 in Montreal, Quebec.

6 Transanal Irrigation for the Management of Low Anterior Resection Syndrome (LARS): A Multicenter Crossover Randomized Controlled Trial

Transanal Irrigation for the Management of Low Anterior Resection Syndrome (LARS): A Multicenter Crossover Randomized Controlled Trial

Study Protocol

Dr. Jessica Holland[1], Shafic Abdulkarim[1], Gordon Best[6], Sarah Saboobeh[2], Marie Demain[2], Dr. Sahir Bhatnagar[3], Dr. Alexander Sender Liberman[1], Dr. Carol-Ann Vasilevsky[1,2], Dr. Nancy Morin[1,2], Dr. Allison Pang[1,2], Dr. Sami Ahmed Chadi[4], Dr Sébastien Drolet[5], Husein Moloo[6], Dr Carl Brown[7], and Dr Marylise Boutros[1,2]

[1]McGill University, Department of Colorectal Surgery, Montréal, QC.
[2]Jewish General Hospital, Division of Colorectal Surgery, Montreal, QC
[3]Department of Epidemiology, Biostatics and Occupation health and the Department of Diagnostic Radiology, McGill University
[4]Toronto Western Hospital, University Health Network, Toronto, ONT
[5]Hôpital Saint-François d'Assise, Centre de Recherche de Québec, Montréal OC
[6]Ottawa Hospital, Univeristy of Ottawa, Ottawa, ONT
[7]St. Paul's Hospital, University of British Columbia, Vancouver, BC

Corresponding Author:

Marylise Boutros, MD, FRCS(C)
Assistant Professor, Department of Surgery, McGill University
Jewish General Hospital, 3755 Cote Ste Catherine G-317, Montreal, QC, H3T 1E2
mboutros@jgh.mcgill.ca

Keywords: Low Anterior resection syndrome (LARS), transanal irrigation (TAI), Study protocol

Abstract:

Introduction: Low anterior resection syndrome (LARS) is a persistent debilitating condition that results from rectal resection. Transanal Irrigation (TAI) is a nonsurgical intervention aimed to improve the symptoms and quality of life (QoL) of patients with LARS.

Methods and Analysis: This multicenter randomized controlled cross-over trial investigates the effect of TAI, taught through a primarily virtual platform, on the QoL and symptoms of participants with significant LARS (LARS score > 20). Participants will be first randomized to either three months of irrigations or to the control group consisting of no mandated change to their current management strategies, after which they will proceed to a one-month washout period, followed by crossing over into the second, alternate arm of the trial. The primary outcome will be an improvement in QoL as measured by the EORTIC-CLC-Q30, and secondary outcomes will include bowel dysfunction as measured by the LARS score and the Cleveland Clinic Fecal Incontinence Score as well as patient-reported satisfaction with their treatment.

Ethics and Dissemination: Ethics approval for this study has been obtained from the Centre Intègre universitaire de santé et de services sociaux (CIUSSS) du Centre-Ouest-de-L'ile-de-Montreal and will be obtained subsequently from all participating institution outside Quebec individually. Results of this trial will be reported as open access in a peer reviewed medical journal.

Registration: ClinicalTrials.gov Identifier NCT05007015
Protocol version: 2022 / July / 01

Strengths and Limitations:

- Study design to elicit patient centered outcomes using a standardized QoL measure
- Unique virtual teaching platform will allow for a wide accessibility for TAI beyond tertiary academic centers
- Cross over design provides a control group with minimal confounding and minimizes the required sample size
- There is a risk of protocol violation if patients decline to stop TAI when their period in the treatment arm comes to an end if the treatment improves their QoL
- TAI requires a motivated patient with the manual dexterity to participate in the intervention and may not be suitable for all patients with LARS

Introduction:

Advances in surgical technique and neoadjuvant care for the treatment of rectal cancer have increased the rate of sphincter preservation and increasing allowed for the restoration of bowel continuity. Unfortunately, these advances have not been without long-term functional consequences for patients (1-4). Following a low anterior resection (LAR), 50 to 75% of patients will experience some degree of bowel dysfunction which has been shown to have a significant negative impact on patients' QoL, which persist indefinitely (5,6). With the incidence of rectal cancer increasing in younger patients, these long-lasting sequalae following restorative proctectomy have an even more profound impact on patients' ability to return to work and their pre-operative functional capacity (7-9).

There is no universal or definitive treatment for LARS, but rather the clinical approach is to manage the individual's symptoms in a stepwise approach beginning with conservative therapies and advancing to increasingly more invasive options (10). Medications, such as anti-diarrheal or bulking agents, and pelvic floor physiotherapy can be used to minimize liquid stool incontinence and to improve functional outcomes. Unfortunately, many patients will still have significant uncontrolled symptoms. As early as 1989, transanal or retrograde colonic irrigation was proposed as a potential treatment for incontinence after anterior resections (11). This non-surgical intervention allows patients to mange their LARS symptoms by preforming a controlled irrigation for colon at a time conveninet for their life. The current evidence for TAI in the management of LARS consistent primarily of small observational trials, and one small randomized controlled trial (11-19). These studies have included a heterogenous population and have been inconsistent in the outcome measured but have demonstrated a reduction of LARS score, overall number of bowel movements per day and some improvement in various QoL measures, with the use of TAI.

Although the current trials are limited in size and design, taken together they represent emerging evidence for the benefit of TAI in LARS and provide the basis for pursuing a larger randomized control trial (RCT) in the North American. This randomized controlled crossover trial aims to evaluate the impact of TAI on QoL and bowel function in participants living with significant bowel dysfunction following rectal surgery. To our knowledge, this is the first North American based trial and the largest RCT on the use of TAI. This will also be the first study to teach and support patients through a primarily virtual platform. We hypothesize that TAI will

allow patients more control over their bowel habits, reduce their LARS symptoms and positively impact participants' QoL. We hope that the results of this trial will allow TAI to become part of the standard armamentarium of clinicians for LARS management, with the presence of online nursing support and guidance to facilitate the wider use of this therapy.

Methods

This is a multi-center, cross-over, pragmatic RCT involving patients recruited from at least five large, academic hospital with active colorectal programs, located in Quebec, British Columbia and Ontario respectively, each with a volume of restorative proctectomies over 30-40/year. This will allow us to feasible recruit sufficient sample size to demonstrate of a benefit of TAI if present. These are primarily academic centers in urban location, but participants' residential geographical location will not be restricted as teaching will be primarily through online portal. The planned sites and their site leads are available in *Appendix 1*.

The crossover design was chosen to allow us to control for the many of the surgery and patient specific factors known to impact the severity of LARS without requiring a sample size that could not be reasonable obtained. TAI is one of the few treatment options available for patients whose symptoms are not controlled with conservative management limiting alternative treatments that could be offered to patients. Other treatments require surgical intervention, including sacral nerve stimulation and or permanent colostomy creation, neither suitable for a control arm of a traditional RTC (10). TAI is an ideal intervention for a cross over trial as it is an acute intervention with time limited effects, and as such there is minimal risk of contamination between the two treatment groups.

Eligibility Criteria:

Participants who meet the following inclusion criteria will be recruited: Adult (≥18 years-old) patients, LARS score ≥20 points, have underwent LAR by a laparoscopic, robotic, transanal total mesorectal excision, or open approach with or without creation of a diverting loop ileostomy for the treatment of rectal cancer, advanced adenoma or dysplasia and have had their ileostomy closed (if applicable) at least six month before entry into the study. Exclusion criteria include: (1) inability to provide informed consent, including fluency in English or French

language (2) unable to access the internet, (3) presence of an ostomy, (4) active or ongoing treatment, (5) anastomotic stricture, sinus or any other ongoing anastomotic complications.

Interventions:

After enrollment into the study, all participants will be mailed a LARS information booklet along with a bowel diary to complete for two weeks to establish their baseline bowel function prior to entry into the study. Other baseline patient reported outcome measures (PROMs) will be completed online or on paper mailed to the participant as per their preference. Participants will then be randomized into one of two cohorts based on the order of their participation in each arm of the study.

Transanal irrigation (TAI) group (intervention):

Upon randomization to the intervention arm of the study, each participant will receive a mailed package of TAI materials, including the device and instructional material, and will be given access to the web-based teaching platform. In previous and ongoing work, our group has created a web-based application with the input of a multidisciplinary group of practitioners which aims to provide educational content and peer-support to rectal cancer survivors with LARS and promote patient engagement, self-management, and well-being. It is accessible on any device with internet access or cellular data. The application has been modified to create a TAI specific version to support the nursing lead teaching. We have removed the peer-support tools, and included access to videos and written instructions on how to perform TA, patient testimonials, and a portal to submit questions to the study team.

Each participant will have two scheduled virtual visits with a trained research nurse to learn how to use TAI within the first two weeks in the intervention arm. These sessions will include one on one session with the nurse for review of the material, discussion of the device and any questions. Additional sessions with the research nurse can be scheduled as needed basis, by phone or in-person consultations. Participants will be instructed to perform TAI daily initially and continue for 3 months.

TAI involves introducing a catheter into the anus connected to an irrigation system which is filled pre-insertion with tap water. An initial volume of 1000 mL will be

suggested but can be increased to 1500mL or reduced to 500 mL as per patient preference and tolerance. The catheters are single-use instruments are disposed into standard waster receptacle after each treatment. The irrigation device (Coloplast Peristeen® anal irrigation system) is designed for multiple uses and participants will be provided with sufficient catheters for the 3-month duration of the intervention arm of the study with regular (daily or every 1-2 days) irrigation. The manufacture recommends disposing of entire system after 90 irrigations and the patients will be instructed to do so. Irrigation can take anywhere between 20 and 90 minutes each session.

Traditional care (control) group:

In the control phase of the trial, participants will have received our educational LARS booklet but will not have any specific modifications to the care they have received prior to commencing the study. They are expected to continue with any prior management techniques or medications prescribed by their clinical team to manage their LARS. Patients already performing irrigation at the direction of their clinical team would not be appropriate for this trial.

A wash out period of one month will occur between cross-over to the next arm of the study. Patients who feel that they are benefiting from the treatment and were randomized into the treatment first cohort, would exit the study should they be unwilling to discontinue the irrigation for the three months of the control arm. If willing, they will be asked to continue to document their experience via the planned PROMs. Their withdrawal from the study and the reason for this withdrawal will be reported. An intention to treat and per protocol analyses will be performed.

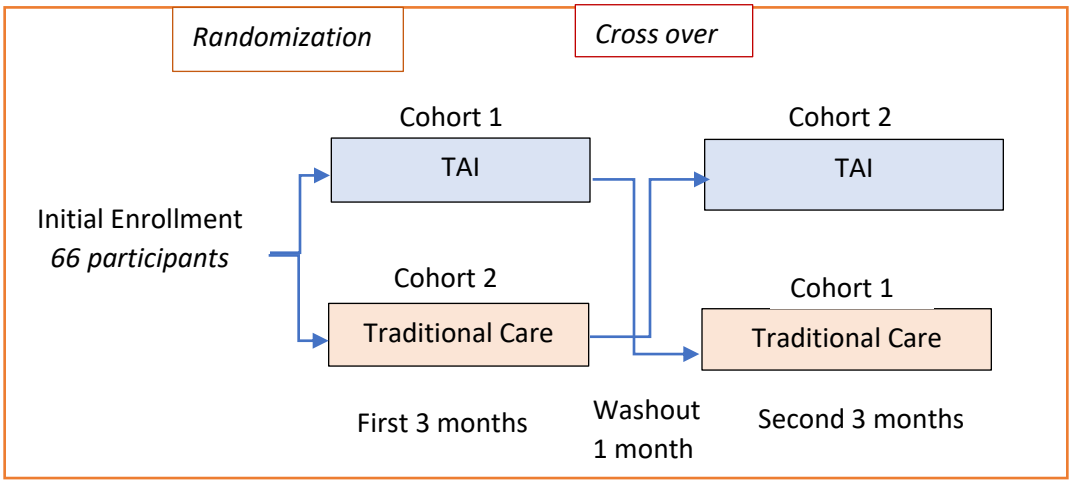

Figure 1 Schematic representation of the structure of the trial

Outcome Measures:

The primary outcome of this study will be a change in global QoL as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30). Secondary outcomes will include a change in bowel function as measured by the LARS score and bowel diaries, incontinence as measured by the Cleveland clinic fecal incontinence score (CCFIS), and patient satisfaction as reported in satisfaction questionnaire and open-ended questions.

Baseline demographics, medical comorbidities, as well as disease and treatment characteristics will be obtained from hospital chart review, including known predictors of poor bowel function, including tumor height, neoadjuvant radiotherapy, reconstruction technique, and history of previous anastomotic leak. The remaining data will be gathered from self-reported questionnaires at the beginning of the study, at completion of each arm and after the washout period. All outcomes for the study will be measured using various PROMs (described below).

PROMs collected include:

- Quality of life: QoL will be measured using the EORTC-QLQ-C30. It consists of 30 questions, which aggregate into one global QoL scale, five functional scales, three symptom scales, and six single items. The EORTC-QLQ-C30 has been well validated in rectal cancer patients and correlates with severity of LARS (2).

- Bowel function: Bowel function will be measured using the LARS Score, a 5-item tool aimed at symptoms of bowel dysfunction, with each question weighted differently according to impact on QoL. The LARS Score allows physicians to categorize patients as having major LARS (30-42 points), minor LARS (21-29 points), or no LARS (0-20 points) (20). We will also be using the CCFIS to measure the degree (if any) of incontinence.

- Satisfaction survey: A satisfaction survey assessing how satisfied participants are with their current bowel function and the treatments will be administered (Appendix 3).

- Bowel Diary: Participants to record the number of bowel movements per day in a bowel diary over a 2-week period as an objective measure of change in frequency of bowel movements. The irrigation will not be counted as a bowel movement.

Detailed schedule of the schedule of PROMS is attached listed in Table 1.

Compliance will treatment protocol will be measure by a patient reports irrigation diary kept during the course of the irrigation arm of the trial. Any continued use of irrigation on at least a weekly basis during this period will be considered a compliant with the treatment. The average pattern of irrigation use will be reported.

Table 1 Timeline of participants PROMs

Phase	PROMS	2 weeks prior to beginning of trial	Start of trial	Month 1	Month 2	Month 3	Washout period 1 month	Month 5	Month 6	Month 7
Cohort 1	Bowel diaries	x				x	x			x
	Satisfaction survey (initial)	x						x		
	Satisfaction survey (irrigation follow up)					x				
	Satisfaction survey (control follow up)									x
	LARS score, EORTIC C30 QoL, CCFIS	x				x		x		x
Cohort 2	Bowel diaries	x				x	x			x
	Satisfaction survey (initial)	x						x		
	Satisfaction survey (irrigation follow up)									x
	Satisfaction survey (control follow up)					x		x		x
	LARS score, EORTIC C30 QoL, CCFIS	x				x		x		x

Participants with be randomized into one of two cohorts. Cohort 1 will include patient randomized to intervention arm first, followed by the control arm. Cohort 2 will include patients randomized to control first, who then will enter into the intervention arm in the second period. PROMs completed on month 3 and month 7 will be completed as near as possible to the end of the month. PROMs completed at the month 5 will be asked at the beginning of the month before entry into the next treatment groups. Bowel diaries will be completed for the last two weeks of the month

Sample Size:

There is no single sample size formula applicable given the multi-faceted aspects of our proposed study design, including a crossover design with two periods and multiple sites, and therefore guidance from a trained biostatistician was sought. Using Monte Carlo simulations, we obtained an estimate of statistical power (21). This requires estimates for each of the fixed effects as well as standard deviations (sd) for the random effect and error term. We used some estimates from the literature; the baseline effect (intercept) used was a QoL of 65, period effect of 5 points, sd for random effect of 5, and sd for error term of 10 (5, 6, 22). In 1000 different simulated datasets of sample size 60 (6 sites with 10 patients/site), we found our study would be able to

detect a 6-point difference, 85.8% of the time (95% CI: 83.48, 87.91). According to the consensus guidelines on use of the EORTC-QLQ-C30 to power an RCT, a mean difference in global QoL of 10 points is the most appropriately expected effect-size for interventions aimed to improve QoL in cancer patients (5, 25). Therefore, the planned sample size of 60 patients will afford good precision.

Given the expected risk for a 10% attrition rate over the study period, the adjusted final sample size is 66 patients in total. We anticipate that we can accrue this patient sample from the five interested sites within a year, given that the participating sites should have several hundred rectal cancer survivors in active surveillance within the first 5 years post treatment (500 – 600 eligible patients) of which at least 50% (250 - 300/site) should have significant LARS. Each site would therefore be expected to recruit 10-15 patients without difficulty.

Recruitment Strategy:

Patients will be introduced to the study by their clinical team, who will clearly explain the objectives of this study and the intervention at a routine follow-up visit a minimum of 6 months after the completion of their treatment. Participants may also be recruited as patients referred to participating colorectal centers for ongoing LARS treatment. The site research coordinator will then reach out to the participant to explain the study in more detail and obtain consent. Consent forms are attached in *Appendix 2*. We anticipant adequate recruitment given the large clinical base at the participating centers and motivation from patients given the significant impact that these symptoms have on their daily lives, without offering any direct financial incentive.

Assignment of interventions:

Following informed consent, eligible participants will be randomized (1:1 ratio) to one of two groups: (1) Transanal Irrigation (Intervention group) or (2) Traditional care (Control group). To yield balanced yet unpredictable groups, randomization will use computer-generated, permuted, balanced blocks of randomly varying size (4 or 6). An online centralized computer-generated randomization sequence will be used to ensure allocation concealment. Randomization will be stratified by hospital site.

There is expected to be minimal contamination between phases of the study as the treatment effects of this intervention are limited to the period when irrigations are performed.

The material will be provided for the 3 months of the irrigations and participants will be instructed to depose of the system itself after 3 months in accordance with manufacturers' recommendations as such the risk of participants continuing with irrigation in the control arms will be minimized.

Blinding of trial participants or outcome assessors is not possible given the nature of the intervention as our primary outcome is patient reported.

Data collection management and analysis:

All data will be collected on a secure web-based electronic data capture software, REDCap. REDCap is hosted and maintained by the Lady Davis Institute of the Jewish General Hospital (JGH). Participants who prefer to complete the PROMs on paper will have a physical copy mailed to them directly and return to the lead study team. The collected data will be kept on a secure, password-protected JGH secure server and paper-based forms will be kept in locked cabinets onsite accessible only to the research team.

A random code number will be assigned to each participant through REDCap. Participants will be identified by the assigned random code to protect their identity. A document linking the codes to the participants' identity will be kept separately in a file with a unique password on the JGH secure institutional server on a password-protected computer at the JGH and will only be accessed by the research team. Personal information will also be kept each on separate files protected by a unique password on the JGH secure institutional server on a password-protected computer at the Jewish General Hospital.

The data will be kept for 25 years according to the institutional policy after 10 years, all data will be anonymized and kept indefinitely. After 10 years, the consent forms will be shredded in the confidential bin provided by the CIUSSS du Centre-Ouest-de-L'ile-de-Montreal. We will also provide the REB with a Nagano message once the data is destroyed, certifying the completion of secure destruction activity.

Statistical Analysis:

Descriptive data will be computed including means with standard deviations, medians with ranges, or frequencies with proportions, where appropriate. The impact of TAI on QoL will be assessed using within-subject differences of health care related QoL between treatment

arms. Specifically, we will use a two-sample, paired t-test. Here, the average within-subject difference of QoL is compared between (1) subjects who received TAI followed by traditional care vs. (2) subjects who received traditional care followed by TAI. We will check the assumption of negligible carryover effects using an unpaired t-test on the within-subject sums of the results from both periods (24).

Monitoring:

No formal data monitoring committee has been formed for this study. Given the short nature of the study no interim analysis is planned. Auditing of the data will be performed on a regular basis by the study team to ensure that PROMs are being collected as per protocol, but no independent audit is planned.

Rectal irrigation via enemas is a common part of the preparation for standard examinations post low anterior resection. However, the protocol will require more routine use of the treatment on a daily basis coupled with a generally larger volume of irrigation. There is a small risk of traumatization of the area, with potential perforation of the rectum, although no incidences of such complication for patient with LARS have been reported in the current literature (11-19). Should a perforation occur, it would be immediately reported to the Jewish General Hospital Research Ethics Board as a serious adverse event. We will minimize this risk by providing teaching on proper applications and have chosen a lower risk population (minimum of 6 months from their surgical resection). Other described side effects of the treatment include minor bleeding, abdominal pain, nausea, and discomfort on insertion of the irrigation device - all of which will be disclosed to the patients - are represent transient symptoms that will resolve with discontinuation of treatment.

The irrigation device, Coloplast Peristeen® anal irrigation system, was originally designed to treat fecal incontinence. Its use in LARS has been demonstrated in other trials but product instructions for use recommend special caution for use if patients with previous anal or colorectal surgery (11-19). Use in this trial will be under medical supervision and we believe in the best interest of the patient given no alternative treatment options are available without greater level of risk. TAI has been shown to be a safe procedure, with a recent global audit reporting a bowel perforation rate of 2-6 per million procedures, nonetheless, it should be introduced with

the support of an experienced healthcare personnel who can provide appropriate instructions and guidance (18).

The irrigations will require a time commitment from each participant. Time on the toilet for treatment will vary between patients but studies have suggested a mean time of approximately 45 minutes with range of 20 to 90 minutes (11, 15). This single time commitment will be overset by expected overall fewer bowel movement and time spent managing their LARS symptoms.

Any incidental finding that are discovered in the course of this study will be disclosed to the patient directly by one of the principal investigators. It will then be shared with their primary care physician or appropriate primary surgeon as requested by the participant for follow up outside of the trial.

Ethics and Dissemination

Ethics approval for this study has been obtained from the CIUSSS du Centre-Ouest-de-L'ile-de-Montreal; this will allow for expedited ethics approval at all the Quebec sites. Ethics approval for additional sites will be obtained separately. Any protocol amendments will be submitted to the review board before being disseminated and reviews as individual participants institutions outside of Montreal.

Participant confidentiality will be respected in compliance with requirements of the Charter of Right and Freedoms of the Civil code of Quebec, and the equivalent relevant legislation in each province participating. Participants will be assigned an arbitrary study ID on entry into the trial and the code linking participants' names to the data will be kept in a locked Excel file accessible only by the principal investigators of the study. Participants' identities will by necessity be known to the research nurse involved in training on TAI.

Funding for this trial has been secured in the form of research grants from the Canadian Society of Colon and Rectal Surgeons ($10 000), the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) 2022 Research Award ($30 000 USD), and the American Society of Colon and Rectal Surgeons ($20 000 USD). A generous donation from the Jewish General Hospital Colorectal Outcomes Research Fund will be used to cover the cost of the devices. These funding sources had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results. The

transanal irrigation devices used in the trial are manufactured by Coloplast Peristeen®. They were purchased through standard institutional purchasing process and the company had no role in the design of this study and will have no role its execution, analysis, interpretation, or decision to publish the results

Reported data will only include aggregated data with respect to their demographics and response to questionnaires presenting a minimal risk identification of any individual participant. At the end of the trial, the results will be submitted for publication in recognized peer review journal. Data may also be shared in preliminary or complete forms at local, national, and international medical and surgical conferences.

Author's contributions:

All authors have contributed to the design of this study.

Declaration of interests

The authors of this study have no relevant conflict of interest to disclose. MB has received a teaching honorarium for Johnson & Johnson.

Appendices :

Appendix 1: Participant site and lead co-investigators
Appendix 2: Consent form for participation in study
Appendix 3: PROMs Patient satisfaction questionnaires

These documents are attached at the end of the manuscript due to length of these documents retained legibility of this report.

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7 Discussion

Transanal irrigation provides a potential non-surgical intervention for the management of LARS. While it is invasive, it is one of the few treatment options available for patients who still have significant symptoms after conservative measures have been exhausted, before they must decide between living with their current functional status or undergoing further surgical interventions, not something to be approached lightly after rectal cancer treatment. Sacral neural modulation is the only other option for these patients before the creation of an end stoma, and this treatment has even less quality evidence behind its use for LARS (21, 27). While this provides a justification for the serious consideration of TAI, rectal cancer survivors deserve to understand the benefits and the limitations of this treatment when approaching a trial of TAI therapy. On the basis of the current evidence as reported in Chapter 1, it is difficult for clinicians to provide a reasonable guidance to patients about what they should expect with TAI or to predict who might benefit the most from TAI. It is with these questions in mind that we have designed the cross over RCT described in chapter 2 of this thesis.

The systematic review completed as the first manuscript in the thesis summarizes the current evidence for TAI. At present there are only small observation studies and one RCT reported on the use of TAI in this manner. These studies are hampered by small sample sizes, lack of standardized outcome measures and heterogenous populations. We were unable to isolate a single standardized outcome measure to provide a summary of the effectiveness of TAI. In the six studies which report a LARS score, all reported an improvement in this measure but only four studies reported the impact of the treatment on QoL and these results were inconsistent. This review provides some evidence for the consideration of TAI for the treatment of LARS but it is insufficient for the inclusion of the recommendation in international treatment guidelines.

Some may argue that if there are few other alternative treatments for LARS, it is less important to fully characterize the impact of TAI beyond establishing its safety. In other words, what is the harm of offering this therapy to all patients with LARS and allow individuals to decide whether it is beneficial for themselves. This line of reasoning ignores the significant costs associated with TAI. There is a significant time commitment to performing TAI on a daily basis as patients will be spending up to 10 hours weekly on the irrigations. There is also the cost of the

devices themselves which will be borne by the patients or the health care system, either through private insurance or public extended coverage programs. Furthermore, a specialized nurse needs to devote time to teach and support patients through the intervention. Rectal cancer treatment and LARS already have a significant negative impact on the financial health of patients, and this is yet another cost which has to be balanced against the potential QoL gained (48). If the devices are covered through insurance, the cost is then transferred back to the overall health care system which clinicians are expected to steward by not wasting funds on ineffective treatments. And finally, it is important that clinicians are able to offer patients a reasonable description of the functional consequences of their treatments and the options for post-operative management if they develop significant LARS. It would be irresponsible to continue to offer a treatment which is not reasonably expected to improve their symptoms or their QoL. It would then delay the offer of alternative treatments even if the alternative is the creation of an end stoma, and in this case, it may encourage a false sense that there are a greater number of treatment options than are currently available to manage LARS, in turn pushing patients toward a sphincter-sparing operation. If a patient's QoL is best served by a stoma, then there should be a frank discussion of this early to avoid prolonged disability and promote a return to an acceptable QoL.

If TAI treatment does not benefit the majority of LARS patients, it may be that there is a specific population who would benefit, such as patients with late major LARS. Identifying these patients is essential to avoid offering an expensive, time consuming option to patients who would not benefit. One of the consistent limitations of the studies in the knowledge synthesis of chapter 1 was small sample sizes which prevent subgroup investigations. We hope to address this in the protocol presented in chapter 2 by using a multi-center and a cross-over design. The multicenter design is essential considering that only about 60 to 70% of patients identified by the treating team as potentially benefiting from TAI will choose to participate (44, 45). By incorporating multiple major colorectal centers, we have accessed a greater number of potential patients. The crossover design will help control for important individual factors known to contribute to LARS. In this way we will bolster the internal validity and applicability of the trial results.

We have chosen to focus primarily on late LARS in this study, as participants have to be at least 6 months from end of their surgical care, for both theoretical and practical reasons. In practical terms, this will mean that patients have a well healed anastomosis and at least one or

two surveillance visits with their surgeons. Since the primary recruitment is by colorectal surgeons, this will allow surgeons some time to identify likely participants at these visits, introduce the idea, and allow potential participants to carefully consider the options before making a decision on pursuing the treatment. This will hopefully increase the likelihood that participants will complete the trial and help with the hesitance to commit to TAI on the initial offer. Given our aim is to offer the treatment primarily through an online platform and to centers outside a restricted geographic area, there is no scheduled in person visits planned which would allow the study team to confirm the anastomosis is intact before beginning the trial. Thus, it is essential that the participants have had this follow-up check with their respective clinical team. From a theoretical perspective, our aim is to address the long-term impact of LARS, especially on patients' QoL including their ability to return to work and pre-diagnosis role functioning. We are therefore focused primarily on late LARS which develops in the time frame that most participants would be recovered from their other oncologic care and be expected to return to pre-treatment function.

The current evidence for TAI has come primarily from European trials. While there is no reason to believe that bowel dysfunction characterized by LARS would be different in other geographic locations, apart from a difference in the proportion of patients who underwent radiation (49) it is reasonable to suppose that there may be a difference in the acceptance of TAI. We expect that the feasibility of TAI in a North American context will have to consider difference cultural backgrounds and different health care systems. In many of the academic centers which ran the trials discussed in the systematic review, established specialized clinics for the screening and treatment of gastrointestinal function disorders, some led by specifically trained nurses, seem to be well-established. This type of clinic is rare in the Canadian context and follow up is often more haphazardly left to individual surgeons or even family physician without specific training in this area. Despite our site partners representing many of the largest rectal cancer treatment centers in the largest urban centers in Canada, none of them have this type of supportive clinic to offer to rectal cancer survivors. North America has a particular geographic challenge of a largely spread-out population with health care resources concentrated in dense populations centers. These factors speak to the importance of a North American centered trial and one that provides a virtual platform to improve access for patients across the continent to these treatment strategies.

The virtual delivery mechanism for teaching TAI is extremely important in the Canadian context if the treatment will be feasibly offered out of a few academic centers. Our LARS virtual platform allows patients to take control of their own health and presents quality, evidence-based, knowledge on the subject. It can be reviewed by patient in the comfort of their own home and in in the time frame that suits them. We hope that it will help patients overcome the initial hesitation with TAI that was observed in a number of the studies identified in our systematic review. It will also provide a mechanism for the adoption of this technique. Even with the most successful clinical trials, there is often a delay in adoption and the translation of knowledge from the academic realm to practice. In creating the teaching platform and a structure for introducing patients to this treatment beyond the duration of this clinical trial, we hope that the barrier to implementation will be minimized.

Finally, one of the most frustrating aspects of the research on the LARS is the lack of standardized outcome measures and definitions in the current literature. It is an understandable limitation given the variations in the clinical presentation of LARS but the ability to follow a syndrome over time, compare treatment options, and synthesis evidence requires some common outcomes measures. We chose to use both the LARS score, the CCFIS, and a two-week bowel diary in our clinical trial design for a direct measure of bowel function. In this way, we hope to be able to contribute objective numbers to a largely subjective syndrome. While the LARS score is a blunt tool, it is also accessible and widely used. It can easily be adopted into clinical practice without excessive demands on patients or clinicians. Until there is an improved scoring system which can compete with these attributes it should be included in any new research published on LARS. The bowel diaries will also provide objective measures in bowel function through items like number of bowel movements per day, nightly bowel movements, and episodes of incontinence allowing us to describe in detail the changes seen with TAI. This is again a simple score which can be compared between sites and trials. The EORTIC-CLC-C30 and the satisfaction questionnaires will make up for some of the limitation in translating LARS score to a clinically relevant outcome. Improving the LARS score or the number of bowel movements is only clinically relevant if it is accompanied by an improved QoL as LARS is not a condition that by itself inevitability results in physiologic harm but rather the harm comes from its impact a patient's ability to function in daily life. The composite outcome used in this detailed RCT protocol address the impact of TAI on participants' QoL.

8 Conclusion

In this thesis, I have completed a systematic review of the current evidence for the use of TAI to manage the gastrointestinal dysfunction that follows rectal resection. Despite this treatment appearing in purposed guidelines and being part of the stepwise approach to LARS management used in the individual center which ran a number of these studies, there is poor quality evidence for its use. The protocol detailed in this thesis provides a comprehensive design of a trial to fill in the current gaps in the evidence for TAI. If this trial provides high quality evidence of the benefit of TAI, we have also created reproducible and widely accessible training and teaching module for the teaching of TAI to patient on a virtual platform. Regardless of the results of the ongoing trial based on this protocol, this work will advance the evidence basis for the treatment of LARS.

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Appendix 1: Participant site and lead co-investigators

SITES	SURGEON SITE LEAD	CONTACT	TITLES
JEWISH GENERAL HOSPITAL	Dr Marlise Boutros	Sarah Faris-Sabboobeh Sarah.Sabboobeh@ladydavis.ca	Staff surgeon Research coordinator
MCGILL UNVERSITY HEALTH CENTER	Dr. Sender Liberman	Anne Mahalia Olivier annemahalia.olivier@muhc.mcgill.ca	Staff surgeon Research coordinator
UNIVERSITY HEALTH NETWORK (TORONTO)	Dr Sami Chadi	Urooj Taqvi Urooj.Taqvi@uhn.ca Zineb Harra Zineb.harra@mail.mcgill.ca	Staff surgeon Research coordinator Resident
CENTRE HOSPITALIER UNIVERSITAIRE DE QUÉBEC (CHUQ)	Dr Sébastien Drolet	Nichole Chabot Nicole.chabot@crchudequebec.ulaval.ca	Staff surgeon Research coordinator
ST PAUL'S HOSPTIAL (VANCOUVER)	Dr Carl Brown	Reeve Liew rliew@providencehealth.bc.ca	Staff surgeon Research coordinator
OTTAWA CIVIC HOSPITAL (OTTAW)	Dr. Husein Moloo	Gordon Best gbest@toh.ca	Staff surgeon Resident
HOPITAL MAISONNEUVE-ROSEMNOT (MONTREAL)	Dr Jean-Sébastien Trépanier	Js.trepanier@umontreal.ca	Staff surgeon

Appendix 2: Consent form for participation in study (English version JGH)

CIUSSS WCMH – Jewish General Hospital
Colorectal Surgery Service
Dr. Marylise Boutros

3755 Côte-Sainte-Catherine Road
Montreal, Quebec, Canada
H3T 1E2

Transanal Irrigation for the Management of Low Anterior Resection Syndrome (LARS): A Multicenter Randomized Controlled Trial

Informed Consent form

Principal Investigator:
Marylise Boutros, MD, FRCS(C)
Assistant Professor, Department of Surgery, McGill University
Jewish General Hospital
3755 Cote Ste Catherine G-317
Montreal, QC, H3T 1E2
mboutros@jgh.mcgill.ca

Co-Investigator (trainee):
Jessica Holland, MD, FRCS(C)
PGY6 Colorectal Surgery, McGill University
Jessica.holland@mail.mcgill.ca

Co-Investigator:
Sarah Sabboobeh, MSc
Research Manager
3755 Cote Ste Catherine A-551
Montreal, QC, H3T 1E2
T: 514-340-8222 ext 25996
Sarah.sabboobeh@ladydavis.ca

1. INTRODUCTION

You are invited to participate in a research study on the management of Low Anterior Rectal Syndrome (LARS) with transanal irrigation (TAI). Take the time to carefully read, understand and think about the information that has been explained and given to you included in this form. If you choose to take part in this research study, we will ask you to sign this consent form.

This form may contain some words or information that you do not understand. We encourage you to ask the researcher responsible for this research study, Dr. Boutros, or a member of the research team all questions that you may have. Ask us to explain all words and information that

are unclear. We have the obligation to answer your questions in such a way that you can understand all the information presented to you.

2. NATURE AND OBJECTIVES OF THIS RESEARCH STUDY

This study is designed to determine if transanal irrigation (TAI) can help control the symptoms of LARS. This treatment has been used in other parts of the world with success in reducing some symptoms and improving the quality of life of patients who experience LARS. You are being asked to participate as you have at least minor LARS symptoms, and the current medical management of your symptoms is not adequate to control your symptoms. We are recruiting patients in Quebec and across Canada to try TAI to see if this treatment will have a benefit on their LARS symptoms and their quality of life.

3. RESEARCH STUDY PROCEDURES

Brief summary on how TAI works:
TAI involves cleaning out the colon with 1000 mL to 1500 mL of tap water. Like an enema, this involves introducing a cone into the anus. This will be attached to an irrigation system filled with water. You do this while sitting on the toilet. The processes take anywhere from 20 to 90 minutes and will need to be done daily. For most patients, this will be the only bowel movement experienced during the day while the treatment is ongoing.

Randomization procedure:
This is a randomized, cross-over controlled study. A "randomized" study means that there are two different groups and you will be placed into one of those groups by random. Depending on which treatment group you are placed in, you will either be asked to continue with your current management plan of LARS (control group) or to try daily irrigation with TAI (treatment group).

A "cross-over" design means that after 3 months of being in one group, you will have a one-month break and then switch groups in order to start treatment in the other group for another 3 months.

The total duration of your participation will thus be 7 months from the time of recruitment.

Transanal Irrigation (Treatment Group):
Participants in the treatment group will receive two teaching sessions on the use of the rectal irrigation system by an Enterostomal therapy nurse (a nurse specializing in the treatment of wounds, ostomy and continence care). These sessions will take place virtually via a secure virtual platform designed specifically for patients with LARS, called "eLARS app". You will receive an e-invite that will take you to the sign-in page of the platform, where you will choose a username and password to access the platform and interact with the nurse. You will have the option to schedule your training sessions with the nurse either through the online platform or by telephone.

On the eLARS app, you will also find more informational material in the form of an illustrated pamphlet and pre-recorded videos on how to do these irrigations.

Participants in this group will also be given the written manufacturer's instructions on how to use the system. If you still have any questions or have problems along the way, follow up can be provided by further meeting on the virtual platform or by phone calls. Physical appointments are also available for those that can travel to Montreal.

Standard of care (control group):
If you are in the control group, no changes will be made to the treatment regime prescribed by the surgeon, which typically includes the usual dietary modification and medications prescribed by the treating team.

Questionnaires and data collected:
Data on your general health, rectal surgery and treatments will be collected at the beginning of the study from you and your hospital chart with your permission. During the study, we will be collecting data on how the treatment is working. We will ask you questions about your bowel function using the validated LARS score and Wexner Fecal Incontinence Score, as well as your quality of life using the validated EORTC-QLQ-C30 questionnaire. We will also ask you to complete a satisfaction survey throughout your participation to get feedback on the intervention. You will be asked to fill out the questionnaires seven times:

1) Before you start the study treatment;
2) After each month of the first treatment (1,2, 3 month of participation);
3) At the end of the pause period and right before you begin treatment in the second group (month 4 of participation);
4) After each month of the second treatment (5, 6, 7 month of participation)

You will also be given a diary to record your bowel movements throughout your participation in the study. We will kindly ask you for a copy of these diaries at the end of your participation.

We may contact you for further details on your feelings about TAI and LARS if you agree to participate further. Participation in this trial will not change the surgeon's role in your health care and treatment. Surgeons will continue to provide the same care they would provide to any of their patients.

4. RISK, INCONVENIENCES AND DISADVANTAGES RELATED TO RESEARCH PARTICIPATION

The TAI irrigation system used in this study is a Peristeen system for anal irrigation not treatment of LARS. This device was designed and approved for management of fecal incontinence and not for LARS treatment, although it has been used in other research for this purpose. Use in this trial will be under medical supervision.

Risks involved in participation in this study are low. Other participants in similar studies have reported abdominal pain and cramps, nausea, discomfort or pain inserting the device in the anus, and minor bleeding associated with irrigation. These symptoms are short term and resolve when you stop the treatment. Perforation (making a hole in the bowel) is a theoretical risk of this treatment but it has not been seen in any trials to date.

We expect that any benefit seen with TAI will last as long as you continue the treatment, as other studies have shown that when you stop the treatment, symptoms come back. Unfortunately, this is not a cure for LARS but a way to manage your symptoms to allow you a better quality of life.

5. POTENTIAL BENEFITS RELATED TO RESEACH PARTICIPATION

The benefit of participation in the study will be access to an alternative treatment, TAI, for the management of your LARS, including the system for the irrigation and training on how to use it. However, we cannot guarantee that you will receive any benefits from this study. Additionally, your participation in this study is likely to help us better answer our research question. This may ultimately influence our approach to patients undergoing this operation and help change the standard of care for this patient population.

6. COMPENSATION

You will receive indirect compensation for participation in this trial: the system required for the irrigation will be provided free of charge. Should the participants withdraw prior to the end of the research study, no cost will fall on you for any material sent to you.

7. CONFIDENTIALITY

As part of this research, we will collect personal information from you (this means information that can identify you). To keep your information private, you will be identified only by a random code. The code key that links your name to your research file will be kept in a secure document only accessible by members of the research team. No data will be published in a way that might identify you. Documents containing your personal information, such the consent form, questionnaires and journals will each be kept in a locked cabinet in a locked office at the CIUSSS du Centre-Ouest-de-l'Île-de-Montreal.

You have a right to access the information we will collect from you during the study. At any point you can request to see your answers to previous questionnaires. You will not be able to see any other participants' responses individually, but you will be able to see the end summary of results in the final publish paper.

All information that may allow you to be identified will be kept at the Jewish General Hospital on a secure hospital server. The information collected from you will be kept for 10 years by the researcher in charge of the research study, after which it will be permanently destroyed following CIUSSS du Centre-Ouest-de-l'Île de Montréal policy.

For monitoring, control, protection and security purposes, your research study file could be checked by persons authorized by the Research Ethics Committee of the CIUSSS du Centre-Ouest-de-l'Île de Montréal or by Jewish General hospital. These persons are bound by a confidentiality agreement.

8. VOLUNTEER PARTICIPATION AND THE RIGHT TO WITHDRAWAL

Your participation in this research study is voluntary and ongoing. You are free to refuse to participate. You may withdraw from this research study at any time without having to give a reason and without any consequence to you now or in the future.

Whether you decide to participate or not, or if you withdraw at any time from this research study, your decision will not affect the quality of care and services that you have the right to receive or your relationship with your doctor in any way.

If you withdraw from this research study before it ends, the information we already collected from you will be kept, unless you ask us to destroy it.

9. NEW INFORMATION ACQUIRED (Incidental Findings)

If we discover any new information on your health, we will tell you everything that we discover and with your permission will disclose that information to your family doctor or colorectal surgeon as appropriate to allow you to receive any necessary treatment.

10. FUTURE USE, COMMUNICATION AND PUBLICATION OF RESEARCH RESULTS

The data collected will be used only for the purposes of research on LARS. With your permission, the data collected from you could be used for future studies on this treatment or other treatment for LARS.

The research study results will be presented as grouped data (results are gathered together). This means that you will not be able to obtain individual results unless you request it directly.

The results may be presented at conferences, published in specialized journals or be the subject of scientific discussions or be used for teaching purposes (if applicable, state if participants will obtain a copy of an academic journal publication or other). We will take all necessary measures to ensure that you are not identified.

11. COMMERICALIZATION OF RESULTS

The results of this study will not be commercialized.

12. INVESTIGATOR COMPENSATION

The researcher in charge of this study will not be compensated in any form. The researcher in charge of this study has been awarded funding from the Canadian Society of Colon and Rectal Surgeons, American Society of Colon and Rectal Surgeons, Society of American Gastrointestinal and Endoscopic surgeons, and Jewish General Hospital Colorectal Outcomes Research funds to help cover the cost of running the study. The funds have been deposited into a research and development account.

13. RESOURCE PERSONS

If you have any questions regarding this research study, you can contact the researcher in charge, Dr Marylise Boutros at:

Dr. Marylise Boutros
Jewish General Hospital
3755 Cote Ste Catherine A-551
Montreal, QC, H3T 1E2
T: 514-340-8222 ext. 28400
mboutros@jgh.mcgill.ca

Or members of the research team:

Jessica Holland, MD, FRCS(C)
PGY6 Colorectal Surgery, McGill University
Jessica.holland@mail.mcgill.ca

Sarah Sabboobeh, Research Manager
3755 Cote Ste Catherine A551
Montreal, QC, H3T 1E2
T: 514-340-8222 ext 25996
Sarah.sabboobeh@ladydavis.ca

For all questions concerning your rights during your participation in this study, or if you have any complaints or comments regarding your experience in taking part in this research study, you can contact the Local Commissioner of Complaints and Quality of Service of the CIUSSS Centre-Ouest-de-l'Île-de-Montréal or the ombudsman of the institution at (514) 340-8222, ex. 24222.

Appendix 3: PROMs Patient satisfaction questionnaires (English version)

Transanal Irrigation for the Management of Low Anterior Resection Syndrome (LARS): Initial Survey

Date of questionnaire: _____

1) Overall, how much is your quality of life influenced by your bowel dysfunction?
   - □ Not at all
   - □ A little
   - □ Some
   - □ A lot

2) When you first heard about this trial, were you eager to participate?
   - □ Not at all
   - □ Not really
   - □ Neutral
   - □ Somewhat
   - □ Very much

3) How would you rate your level of anxiety regarding the irrigation procedures prior to your first attempt?
   - □ None at all
   - □ Mild anxiety
   - □ Moderate anxiety
   - □ Extreme anxiety

4) How would you rate your level of anxiety regarding your bowel movements during the last month?
   - □ None at all
   - □ Mild anxiety
   - □ Moderate anxiety
   - □ Extreme anxiety

5) How many bowel movements did you have on an average day (for 24hours, including at night) in the last month?
   - □ 1-2
   - □ 3-4
   - □ 5-6
   - □ More than 6

6) How many bowel movements did you have on average during the night in the last month?
   - □ 1-2
   - □ 3-4
   - □ 5-6
   - □ More than 6

7) Do your LARS symptoms affect your ability to carry out your regular daily activities?
   - □ Not at all
   - □ A little
   - □ Somewhat

□ A lot
□ Completely

8) Have your LARS symptoms prevented you from returning to your previous employment?
□ Yes
□ No
□ Not Applicable

9) If you have returned to work since your surgery, have you had to miss work to manage your bowel functions? If so, how many half-days did you miss in the last month?
_____ half-days

10) If you have returned to work since your surgery, you may have had to leave early as a result of your bowel functions. If so, how many half-days did you miss in the last month?
_____ half-days

11) How long each do you spend in the bathroom each day?
_____ minutes

12) Below is a list of symptoms associated with LARS that can impact your life. Please rank in order of most disruptive (1) to least disruptive (8) for you.

☐ Variable, unpredictable bowel function

☐ Altered stool consistency

☐ Increased stool frequency

☐ Repeated painful stools

☐ Emptying Difficulties

☐ Urgent bowel movements

☐ Accidental leakage / Incontinence

☐ Soiling of your undergarments

13) Do you currently feel dependent on quick access to a toilet?
□ Not at all
□ A little
□ Somewhat
□ A lot
□ Completely

14) Do you currently feel preoccupied with your bowel function?
□ Not at all
□ A little
□ Somewhat
□ A lot
□ Completely

15) What is your overall satisfaction with your bowel function?
□ Extremely satisfied
□ Satisfied

□ Neutral
□ Dissatisfied
□ Extremely dissatisfied

16) What is your overall satisfaction with strategies and compromises you have had to make in your daily life to manage your bowel function?

□ Extremely satisfied
□ Satisfied
□ Neutral
□ Dissatisfied
□ Extremely dissatisfied

17) What is your overall satisfaction with the impact your bowel function has had your mental and emotional wellbeing?

□ Extremely satisfied
□ Satisfied
□ Neutral
□ Dissatisfied
□ Extremely dissatisfied

18) What is your overall satisfaction with the impact your bowel function has had your social and daily activities?

□ Extremely satisfied
□ Satisfied
□ Neutral
□ Dissatisfied
□ Extremely dissatisfied

19) What is your overall satisfaction with the impact your bowel function has had your relationships and intimacy?

□ Extremely satisfied
□ Satisfied
□ Neutral
□ Dissatisfied
□ Extremely dissatisfied

20) What is your overall satisfaction with the impact your bowel function has had roles, commitments, and responsibilities in your life?

□ Extremely satisfied
□ Satisfied
□ Neutral
□ Dissatisfied
□ Extremely dissatisfied

Transanal Irrigation for the Management of Low Anterior Resection Syndrome (LARS): Satisfaction Survey – During Irrigations

Date of questionnaire: _____

1) Overall, how much is your quality of life influenced by your bowel dysfunction?

□ Not at all

□ A little
□ Some
□ A lot

2) How would you rate your level of anxiety regarding the irrigation procedures after your first attempt?

□ None at all
□ Mild anxiety
□ Moderate anxiety
□ Extreme anxiety

3) How would you rate your level of anxiety regarding your bowel movements during the last month?

□ None at all
□ Mild anxiety
□ Moderate anxiety
□ Extreme anxiety

4) How many bowel movements did you have during an average day (for 24hours, including at night) in the last month?

□ 1-2
□ 3-4
□ 5-6
□ More than 6

5) How many bowel movements did you have on average during the night in the last month?

□ 1-2
□ 3-4
□ 5-6
□ More than 6

6) Do your LARS symptoms affect your ability to carry out your regular daily activities?

□ Not at all
□ A little
□ Somewhat
□ A lot
□ Completely

7) If you have returned to work since your surgery, do you have to miss work to manage your bowel functions? If so, how many half-days did you miss in the last month? ____ half-days

8) If you have returned to work since your surgery, you may have had to leave early as a result of your bowel functions. If so, how many half-days did you miss in the last month? _____ half-days

9) How long each do you spend in the bathroom each day?_____ minutes

10) How long each day do the irrigation take? _____ minutes

11) What were the biggest issues related to the irrigation?
Please check all that apply.

□ Abdominal cramps and pain
□ Nausea/vomiting
□ Urgent bowel movements
□ Accidental leakage

- □ Time off work or other daily activities
- □ Difficulty using the irrigation device
- □ Time commitment
- □ Scheduling the sessions
- □ Other? Please describe:_____

12) Did you feel that the irrigation helped improve satisfaction with your bowel function?

- □ Not at all
- □ A little
- □ Somewhat
- □ A lot
- □ Completely

13) How was your overall experience with the irrigation?

- □ Extremely satisfied
- □ Satisfied
- □ Neutral
- □ Dissatisfied
- □ Extremely dissatisfied

14) Below is a list of symptoms associated with LARS that can impact your life. Please rank in order of most disruptive (1) to least disruptive (8) for you.

- ☐ Variable, unpredictable bowel function
- ☐ Altered stool consistency
- ☐ Increased stool frequency
- ☐ Repeated painful stools
- ☐ Emptying Difficulties
- ☐ Urgent bowel movements
- ☐ Accidental leakage / Incontinence
- ☐ Soiling of your undergarments

15) Did you currently feel dependent on quick access to a toilet?

- □ Not at all
- □ A little
- □ Somewhat
- □ A lot
- □ Completely

16) Did you currently feel preoccupied with your bowel function?

- □ Not at all
- □ A little
- □ Somewhat
- □ A lot
- □ Completely

17) How was your overall satisfaction with your bowel function?

- □ Extremely satisfied
- □ Satisfied
- □ Neutral
- □ Dissatisfied
- □ Extremely dissatisfied

18) How is your overall satisfaction with strategies and compromises you have had to make in your daily life to manage your bowel function?

- □ Extremely satisfied
- □ Satisfied
- □ Neutral
- □ Dissatisfied
- □ Extremely dissatisfied

19) How is your overall satisfaction with the impact your bowel function has had your mental and emotional wellbeing?

- □ Extremely satisfied
- □ Satisfied
- □ Neutral
- □ Dissatisfied
- □ Extremely dissatisfied

20) How is your overall satisfaction with the impact your bowel function has had your social and daily activities?

- □ Extremely satisfied
- □ Satisfied
- □ Neutral
- □ Dissatisfied
- □ Extremely dissatisfied

21) How is your overall satisfaction with the impact your bowel function has had your relationships and intimacy?

- □ Extremely satisfied
- □ Satisfied
- □ Neutral
- □ Dissatisfied
- □ Extremely dissatisfied

22) How is your overall satisfaction with the impact your bowel function has had roles, commitments, and responsibilities?

- □ Extremely satisfied
- □ Satisfied
- □ Neutral
- □ Dissatisfied
- □ Extremely dissatisfied

31) In your own words, please tell us about your experience with the irrigation treatments.

_____

32) Do you plan on continuing with the irrigation treatments after this trial is completed? Why or why not? _____

33) If you have anything else that you would like the study team to know, please describe in the textbox below. _____

Transanal Irrigation for the Management of Low Anterior Resection Syndrome (LARS): Satisfaction Survey – Control

Date of questionnaire: _____

1) Overall, how much is your quality of life influenced by your bowel dysfunction?
   - ☐ Not at all
   - ☐ A little
   - ☐ Some
   - ☐ A lot
2) How would you rate your level of anxiety regarding your bowel movements during the last month?
   - ☐ None at all
   - ☐ Mild anxiety
   - ☐ Moderate anxiety
   - ☐ Extreme anxiety
3) How many bowel movements did you have on average during day *(for 24hours, including at night)* in the last month?
   - ☐ 1-2
   - ☐ 3-4
   - ☐ 5-6
   - ☐ More than 6
4) How many bowel movements did you have on average during *the night* in the last month?
   - ☐ 1-2
   - ☐ 3-4
   - ☐ 5-6
   - ☐ More than 6
5) Do your LARS symptoms this affect your ability to carry out your regular daily activities?
   - ☐ Not at all
   - ☐ A little
   - ☐ Somewhat
   - ☐ A lot
   - ☐ Completely
6) If you have returned to work since your surgery, do you have *to miss* work to manage your bowel functions? If so, how many half-days did you miss in the last month? _____ half-days
7) If you have returned to work since your surgery, you may have had *to leave early* as a result of your bowel functions. If so, how many half-days did you miss in the last month? _____ half-days
8) How long each do you spend in the bathroom each day? _____ minutes

9) Below is a list of symptoms associated with LARS that can impact your life. Please rank in order of most disruptive (1) to least disruptive (8) for you.

☐ Variable, unpredictable bowel function

☐ Altered stool consistency

☐ Increased stool frequency

☐ Repeated painful stools

☐ Emptying Difficulties

☐ Urgent bowel movements

☐ Accidental leakage / Incontinence

☐ Soiling of your undergarments

10) Do you currently feel dependent on quick access to a toilet?
- ☐ Not at all
- ☐ A little
- ☐ Somewhat
- ☐ A lot
- ☐ Completely

11) Do you currently feel preoccupied with your bowel function?
- ☐ Not at all
- ☐ A little
- ☐ Somewhat
- ☐ A lot
- ☐ Completely

12) What is your overall satisfaction with your bowel function?
- ☐ Extremely satisfied
- ☐ Satisfied
- ☐ Neutral
- ☐ Dissatisfied
- ☐ Extremely dissatisfied

13) What is your overall satisfaction with strategies and compromised you have had to make in your daily life to manage your bowel function?
- ☐ Extremely satisfied
- ☐ Satisfied
- ☐ Neutral
- ☐ Dissatisfied
- ☐ Extremely dissatisfied

14) What is your overall satisfaction with the impact your bowel function has had your mental and emotional wellbeing?
- ☐ Extremely satisfied
- ☐ Satisfied

- ☐ Neutral
- ☐ Dissatisfied
- ☐ Extremely dissatisfied

15) What is your overall satisfaction with the impact your bowel function has had your social and daily activities?
    - ☐ Extremely satisfied
    - ☐ Satisfied
    - ☐ Neutral
    - ☐ Dissatisfied
    - ☐ Extremely dissatisfied
16) What is your overall satisfaction with the impact your bowel function has had your relationships and intimacy?
    - ☐ Extremely satisfied
    - ☐ Satisfied
    - ☐ Neutral
    - ☐ Dissatisfied
    - ☐ Extremely dissatisfied
17) What is your overall satisfaction with the impact your bowel function has had roles, commitments, and responsibilities in your life?
    - ☐ Extremely satisfied
    - ☐ Satisfied
    - ☐ Neutral
    - ☐ Dissatisfied
    - ☐ Extremely dissatisfied
18) Have you used any irrigation in the last three months during the control period? Yes / No
19) If so, what led you to continuing with the irrigations?
    _____
20) If you have anything else that you would like the study team to know, please describe in the textbox below. _____

Transanal Irrigation for the Management of Low Anterior Resection Syndrome (LARS): Qualitative Questions – Washout

1) Have you used irrigation in the last month, during the washout period? Yes / No
2) If so, what led you to continuing with the irrigations? _____
3) If you have anything else that you would like the study team to know, please describe in the textbox below. _____