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Development and Evaluation of a Patient-Centered Program for Low Anterior Resection Syndrome: Protocol for a Randomized Controlled Trial

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ABSTRACT

Introduction: Low Anterior Resection Syndrome (LARS) affects the majority of individuals following restorative proctectomy for rectal cancer. The management of LARS includes personalized troubleshooting and effective self-management behaviors. Thus, affected individuals need to be well informed and appropriately engaged in their own LARS management. This manuscript describes the development of a LARS Patient-Centered Program (LPCP) and the study protocol for its evaluation in a randomized controlled trial.

Methods and Analysis: This will be a multicenter, randomized, assessor-blind, parallel-groups, pragmatic trial evaluating the impact of a LPCP, consisting of an informational booklet, patient diaries, and nurse support, on patient-reported outcomes after restorative proctectomy for rectal cancer. The informational booklet was developed by a multidisciplinary LARS team, and was vetted in focus groups and semi-structured interviews involving patients, caregivers, and healthcare professionals. The primary outcome will be global quality of life (QoL), as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (QLQ-C30), at 6 months after surgery. The treatment effect on global QOL will be modeled using generalized estimating equations. Secondary outcomes include patient activation, bowel function measures, emotional distress, knowledge about LARS, and satisfaction with the LPCP.

Ethics and Dissemination: The Research Ethics Committee at the Integrated Health and Social Services Network (CIUSSS) for West-Central Montreal (health network responsible for the Jewish General Hospital) has approved the study protocol in its current format (MP-05-2019-1628). Collaborating sites are currently submitting the protocol for approval with their local ethics committees, and will not begin patient recruitment until full approval is obtained. The

results of this study will be presented at national and international conferences, and a manuscript with results will be submitted for publication in a high-impact peer-reviewed journal.

Registration: This trial was registered on clinicaltrials.gov on February 4, 2019 (no: NCT03828318).

Strengths and Limitations of the Study

- This will be the first randomized controlled trial evaluating a supportive intervention for patients with Low Anterior Resection Syndrome
- This study will collect longitudinal data on patient-reported outcomes following restorative proctectomy, and will report on the natural evolution of several important outcome measures over the first postoperative year
- The informational booklet used in the trial underwent a rigorous pre-trial assessment and was revised into its final format based on feedback obtained in focus groups involving patients, caregivers, and healthcare professionals
- As with any longitudinal study, there is a risk for attrition throughout the study period, which could be a source of bias in the final results
- Management in the standard care group will vary by institution; however, none of the participating institutions have a formal LARS program for rectal cancer survivors

INTRODUCTION

Restorative proctectomy is increasingly performed for rectal cancer as surgeons continue to push the limits of sphincter preservation.[1,2] However, despite avoiding a permanent ostomy, many individuals are left with significant bowel dysfunction after sphincter-sparing surgery. Low Anterior Resection Syndrome (LARS) encompasses a series of negative bowel symptoms, such as frequency, urgency, incontinence, and clustering of bowel movements,[3] that can affect 70 to 90% of patients following restorative proctectomy.[4,5] Although symptoms may improve somewhat in the first year or two after surgery, long-term bowel dysfunction often remains in more than 70% of patients and major dysfunction in over 50%.[6-8] As such, LARS remains a significant concern for rectal cancer survivors and their significant others, as increased severity correlates with worse perceived global health status and quality of life (QoL).[5,8,9]

Currently, there is no well-established treatment strategy for LARS, and management is both empirical and symptom-based.[4] LARS is usually managed with a combination of lifestyle, pharmacological, and at times, interventional strategies, with mixed success. Due to the individual nature of each patient's cluster of symptoms, much of the care requires personalized troubleshooting and self-management behaviors to improve bowel symptoms and QoL.[4] These behaviors include understanding one's own symptoms, knowing how to use and dose stool bulking agents and anti-diarrheal medications, performing pelvic floor exercises, adhering to dietary recommendations, proper perianal skin management, and preparing ahead of social engagements. Thus, individuals need to be well informed, motivated and engaged in their own LARS management to take more control over their bowel function and achieve optimal outcomes.

Among individuals undergoing rectal resection with a permanent ostomy (e.g., abdominoperineal resection), there is evidence that supportive and informational interventions improve QoL, ostomy proficiency, self-efficacy and knowledge.[10-12] However, evidence regarding the impact of such interventions in patients who undergo restorative proctectomy is lacking, despite the latter operation being far more frequently performed.[1] When provided with the means to better understand and control important aspects of their bowel function, patients may be more likely to experience positive improvements in self-reported outcomes. In a recent review comparing long-term patient-reported outcomes after ostomy or sphincter-sparing surgery for low rectal cancer, the authors concluded that interventions geared towards patients without ostomies warrant further attention.[13]

This paper describes a study protocol for a randomized controlled trial (RCT) investigating the impact of a LARS Patient-Centered Program (LPCP) on patient-reported outcomes after restorative proctectomy for rectal cancer. Furthermore, qualitative data are presented that were gathered through a focus group assembling individuals with LARS and their caregivers, and through semi-structured interviews with rectal cancer healthcare professionals, as a joint effort to develop the LPCP.

METHODS AND ANALYSIS

Phase 1: Study Protocol for Proposed RCT

The study protocol was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.[14]

Objectives

The overall objective of this study is to evaluate the effects of a LCPC on patient-reported outcome measures (PROMs) after restorative proctectomy for rectal cancer. Specifically, our primary objective is to evaluate the extent to which a LPCP improves global QoL, as measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core 30 (QLQ-C30), at 6 months after surgery in comparison to standard care. Secondary objectives include the effects of a LPCP on patient activation, bowel function, emotional distress and patient knowledge.

Participants and Setting

This multicenter RCT involves participants from multiple institutions across North America with high-volume Colorectal Surgery or Surgical Oncology practices. Patients who have undergone restorative proctectomy for neoplastic disease (benign or malignant) located in the rectum (0-15cm from the anal verge) with a diverting ostomy and who are scheduled for ostomy closure are eligible for inclusion. Patients will be recruited approximately one month prior to ostomy closure by their individual surgeon, who will go through the informed consent process with them. Exclusion criteria include: 1) active chemotherapy or radiotherapy treatment at the time of consent; 2) major colonic resection in addition to proctectomy; 3) inability to be contacted by telephone; 4) inability to read and comprehend English or French; and 5) inability to provide clear and informed consent.

Randomization

Consecutive participants will be randomized in a 1:1 ratio into one of two groups: 1) LARS Patient-Centered Program; or 2) Standard Care. Block randomization with randomly varying block sizes will be performed to ensure an equal number of participants in each group.

Randomization will also be stratified by participating institution. An online centralized computer-generated randomization sequence will be used to ensure allocation concealment.

LARS Patient-Centered Program

The LPCP consists of an informational booklet, patient diaries, and nursing support made available only to patients randomized to the intervention group.

1. Informational Booklet and Patient Diaries:

The goals of the booklet are to inform individuals with rectal cancer about postoperative bowel dysfunction, manage expectations, and review the different treatment strategies. Prior to developing the booklet, our team conducted a systematic review of online health information for LARS to assess the readability, suitability, quality, accuracy and content of materials currently available to patients.[15] We concluded that the current body of health information for patients with LARS is suboptimal. In particular, no patient material was written at the American Medical Association-recommended 6th grade reading level, there was little use of headings, summaries and illustrations to accompany the text, and important content was missing. We then set out to develop our own informational booklet, drawing on the important elements emphasized in each assessment tool used in the systematic review. After developing the first draft of the booklet, patients, caregivers, and healthcare professionals provided feedback to improve the booklet into its current format. A more thorough description of the booklet's development process can be found below (see Phase 2 below).

The booklet will be introduced to patients at the time of study recruitment (before ostomy closure). Participants will be instructed to read through the booklet at least once prior to their ostomy closure operation and will be encouraged to consult it as much as needed thereafter. In addition to the informational booklet, participants will receive Bowel Symptom, Diet, and

Loperamide diaries and will be instructed to use them whenever experiencing any symptoms of bowel dysfunction, and for 2 weeks prior to each scheduled nurse phone call (please see the next section below). The goal of these diaries is to assist participants in recognizing the underlying patterns related to their symptoms so that they can optimize their self-management.

2. Nursing Support:

Nursing support will be centralized from one institution and made available to participants in the intervention group, by telephone and email. The study nurse has expertise in rectal cancer management and postoperative bowel dysfunction. She will briefly review the booklet content with participants by telephone at the beginning of the study (prior to ostomy closure) and answer related questions. Postoperatively, the nurse will have scheduled telephone calls with participants at 1-, 3-, 6-, 9-, and 12-months, to provide support and periodically review their completed diaries for troubleshooting. Lastly, she will be available to speak with participants in between scheduled calls, either by phone or by email.

Standard Care Group

Participants randomized to the standard care group will not have access to either the informational booklet nor nursing support. Instead, they will only receive a paper copy (and/or instructions for online access) of the Colorectal Cancer Association of Canada (CCAC) module on "Living with Colorectal Cancer". The standard care group will also receive the usual care for LARS information and counseling that is routinely made available at their hospital, with participating hospitals asked to provide a description of what constitutes "standard care" for LARS. Due to the expected heterogeneity in institutional LARS practices, participating institutions will be accounted for in the final statistical model in addition to stratified randomization by institution.

Data Collection

Baseline demographics, medical comorbidities, and disease and treatment characteristics will be obtained from chart review, including known predictors of bowel dysfunction (e.g., tumor height, neoadjuvant radiotherapy, type of proctectomy [total vs. partial mesorectal excision], reconstruction technique [straight anastomosis vs. neorectal reservoir], and anastomotic leak after proctectomy). The remaining data will be gathered from self-reported questionnaires at study time-points throughout the 12-month study period.

Outcomes

Outcomes will be measured with the use of various PROMs and recorded into an online registry (REDCap) by a blinded assessor. PROMs captured at the same time-point will be completed as a single package. The schedule for all PROMs can be found in Table 1. The PROM package for each time-point will either be mailed to participants, disseminated via email, or completed over the phone, depending on participants' preferences. Participants will receive email and telephone reminders for incomplete questionnaires. The study timeline for both groups can be found in Figures 1 and 2. The following outcomes and PROMs will be collected:

1. Quality of Life:

QoL will be measured using the EORTC-QLQ-C30, a self-report questionnaire developed to assess QoL for patients living with or beyond cancer. It consists of 30 items, which aggregate into 1 global QoL scale, 5 functional scales, 3 symptom scales, and 6 single items. The EORTC-QLQ-C30 has been well validated in individuals with rectal cancer and correlates significantly with LARS severity.[5,8,9]

2. Symptom Changes:

The Measure Your Medical Outcome Profile (MYMOP2) is a patient-centered measure that assesses changes over time in a specific symptom identified as most bothersome to the patient.[16,17] The patient also identifies a daily activity that is being restricted or prevented by the symptom. Both the symptom and the activity are scored using a 6-point Likert-type scale in the last week.

3. Patient Activation:

The Patient Activation Measure-13 (PAM-13) is a 13-item questionnaire aimed at determining the degree knowledge, skills, and confidence for self-management of healthcare.[18] Responses are based on a Likert scale ranging from "disagree strongly" to "agree strongly", and the final score is a transformation ranging from 0 to 100 according to a conversion formula provided by the developers. Activation is then categorized into 1 of 4 groups based on their transformed score: Level 1, "overwhelmed and not ready to take an active role" (≤47.0); Level 2, "realize they have a role to play, but lack the knowledge and confidence" (47.1-55.1); Level 3, "beginning to take action, but still lack confidence" (55.2-72.4); Level 4, "can manage their healthcare, but may struggle to maintain the behaviors" (≥72.5).

4. Bowel Function:

Bowel function will be measured postoperatively using three validated tools/questions. The LARS Score is a 5-item tool aimed at symptoms of bowel dysfunction, with each question weighted differently according to the perceived importance by patients. The scores of the 5 questions sum to 42 points. The LARS Score allows the categorization of patients as having major (30-42 points), minor (21-29 points), or no LARS (0-20 points). The Cleveland Clinic Florida / Wexner Fecal Incontinence Score (WFIS) is a 5-item tool aimed at measuring the

frequency of incontinence to gas and liquid or solid stools, and its consequences (pad wearing and lifestyle alterations). Each question ranges from 0 (never) to 4 (always) and the total score is measured out of 20. Lastly, each participant will be asked a single, validated, bowel-related QoL question: "Overall, how much does your bowel function affect your quality of life?" Responses categorize respondents into 1 of 3 grades: "not at all" (no impairment); "very little" (minor impairment); "somewhat" or "a lot" (major impairment). Bowel-related QoL is significantly correlated with both the LARS Score and general QoL as per previous studies.[9]

5. Emotional Distress:

Emotional distress will be measured using the Hospital Anxiety and Depression Scale (HADS), which has been validated in colorectal cancer survivors.[19,20] It includes 7 items aimed at assessing depression and 7 items for anxiety. Each item is scored 0-3, and is based on frequency of symptoms. The total score is out of 21, and individuals can be categorized as "normal" (0-7), "borderline abnormal" (8-10), or "abnormal" i.e., depressed or anxious (11-21).

6. Knowledge:

Knowledge related to LARS will be measured using a short, investigator-generated, multiple-choice questionnaire. The items reflect key concepts in etiology/risk factors and management of LARS.

7. Satisfaction:

Satisfaction related to the LPCP (information and support related to LARS) will be assessed using a short, investigator-generated, 2-item questionnaire. Responses will be recorded using a 5-point Likert scale, ranging from "not satisfied" (1) to "very satisfied" (5).

Statistical Analysis

Descriptive analyses will include means with standard deviations, medians with ranges, or frequencies with proportions, where appropriate. Continuous outcomes will be compared using a t-test or Wilcoxon rank-sum test and categorical outcomes using χ^2 tests. The treatment effect on global QoL will be modeled using generalized estimating equations (GEE).[21] This method accounts for 1) the within-subject correlation between responses at different time-points, and 2) possible clustering of responses among patients from the same hospital. GEE models also make use of all the available data, so that patients can contribute to the model if they have data available for any single time-point. An appropriate correlation structure will be chosen using the quasi-likelihood information criterion. The effect size, standard error, and 95% confidence interval for the estimate of the treatment effect at 6 months will be reported.

Power Analysis and Sample Size Calculations

The primary outcome of the study is global QoL at 6 months, as measured by the EORTC QLQ-C30. Based on the largest available cohort of patients with QoL data who have undergone restorative proctectomy for rectal cancer and who are ostomy-free, mean global QoL score is assumed to be 77 (maximum possible score is 100) with a standard deviation of 19.[9] According to the consensus guidelines on the use of the EORTC QLQ-C30 to power a randomized controlled trial, a mean difference in global QoL of 10 points (small-medium treatment effect) is the most appropriate expected effect-size for interventions aimed to improve QoL in cancer patients.[22] Thus, with an alpha=0.05 and power=0.80, we estimate that 45 participants are required in each arm of our study. Given the risk for attrition over the 6-month study period, the adjusted final sample size accounting for a 30% attrition rate is 64 participants in each arm (128 patients in total).

Registration

This trial was registered on clinicaltrials.gov on February 4, 2019 (no: NCT03828318).

Phase 2: Development of Informational Booklet

The first draft of the informational booklet was developed by a multidisciplinary team of healthcare professionals who care for patients with rectal cancer. The initiative was co-lead by a General Surgery resident (R.G.) and a Colorectal Surgery attending (M.B.), and included a senior colorectal cancer oncology pivot nurse, pelvic physiotherapist, and members of the McGill University Patient Education Office. The booklet was designed to review important information regarding the epidemiology, symptomatology, and management of LARS. The booklet was written at a 6th-grade reading level, which is recommended by the American Medical Association for any patient material,[23] and included original illustrations designed by our team.

An Institutional Review Board-approved qualitative study was subsequently undertaken to evaluate the booklet. A single focus group with rectal cancer patients and their caregivers, as well as individual semi-structured telephone interviews with healthcare professionals, were conducted.

Participants for the focus group were recruited from individual Colorectal Surgeons practicing at a single institution. The focus group included 12 participants (six patients and their caregivers/partners) and followed a semi-structured interview guide. Each patient was a minimum of 6-months removed from ileostomy closure (if diverted) or proctectomy. Participants' characteristics are reported in Table 2. The purpose of the focus group was to obtain feedback regarding the first draft of the booklet, to better understand participants' current/past experiences with LARS, and to incorporate changes into the booklet to meet the informational needs of rectal cancer survivors. The focus group was audio-recorded and transcribed, and data

were analyzed using the grounded theory.[24,25] The constant comparative method was applied; data from participants were coded based on emerging patterns, concepts, and themes to generate theory, which was then analyzed and categorized accordingly so that descriptive statements could be formed.[25] The principal findings from the thematic analysis of the focus group are displayed in Table 3. Patients described the emotional difficulties of living with LARS and the general lack of support and preparation they received from their healthcare team. They unanimously supported the development and dissemination of the booklet, reporting that it would have had a major impact on their outlook and knowledge regarding LARS in their first year after surgery. Some of the feedback included more emphasis to be placed on expectation management and emotional support, and they asked for more detail regarding enema use. They also requested a list of healthcare providers who could support them in their LARS care, and more examples for foods which may activate their LARS.

Healthcare professionals from multiple institutions across North America were invited to review the booklet as well. In total, 10 healthcare professionals comprised of seven Colorectal Surgeons and three nurses in Gatrointestinal Oncology, and each was interviewed using a semi-structured interview guide. Characteristics of the healthcare professionals are reported in Table 4. The focus of these interviews was largely on content and management strategies; to ensure that our booklet would be as comprehensive and inclusive as possible. Furthermore, healthcare professionals were asked about the layout and structure, clinical applicability, and other means of improving the booklet. Similar to the focus group, the interviews were recorded, and the same methods were used for data analysis. The principal findings from the interviews are displayed in Table 5. Healthcare professionals felt that the booklet was accurate and comprehensive, and that it would compliment the role of a clinician/nurse in supporting patients with LARS. Several

interviewees recommended additional medications and illustrations, but did not feel the layout or structure needed to be further revised. Small changes in language were recommended as well (e.g., "stoma" instead of "bag" – most healthcare professionals felt that patients understand the meaning of stoma).

Based on the results of this qualitative study, the informational booklet was modified into its final format.

Patient and Public Involvement

Patients were involved in the development of the informational booklet to be used as part of the LPCP. Patients and the public were not involved in the design of the study; however, the outcomes proposed in this study are specifically designed to assess participants' experience with LARS and the LPCP. The authors would also like to thank Dr.'s Steven D. Wexner, Patricia Sylla, Mitchell Bernstein, as well as Holly Bonnette and Tracy Chornopyski, for their contributions.

Ethics and Dissemination

The Research Ethics Committee at the Integrated Health and Social Services Network (CIUSSS) for West-Central Montreal (health network responsible for the Jewish General Hospital) has approved the study protocol in its current format (MP-05-2019-1628). Collaborating sites are currently submitting the protocol for approval with their local ethics committees, and will not begin to recruit patients until full approval is obtained.

The results of this study will be presented at national and international meetings, and a manuscript will be submitted for publication in a high-impact peer-reviewed journal. We

anticipate that the findings will inform the development of future rectal cancer survivorship programs with a focus on bowel dysfunction, in an effort to improve the long-term QoL of individuals with rectal cancer.

Data Sharing Statement

At completion of the trial, relevant deidentified participant data will be made available upon request (from the corresponding author, M.B.). The data may be re-used only upon strict permission from the corresponding author.

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Author Contributions

RG, CGL, JP, JFJ, LGB, ASL, NM, JF, GG, CAV, SRB, and MB contributed to the design of the study. RG, CGL, JP, LGB, ASL, NM, JF, GG, CAV, and MB participated in qualitative data acquisition. RG, CGL, JFJ, SRB, and MB contributed to the data analysis plan. RG, JP, LGB, ASL, NM, JF, GG, CAV, and MB were involved in obtaining ethical approval. RG and MB prepared the first draft of the manuscript. RG, CGL, JP, JFJ, LGB, ASL, NM, JF, GG, CAV, SRB, and MB contributed to, and approved, the final version of the manuscript.

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Competing Interests Statement

ASL receives travel stipends from Merck and Servier, and is on the advisory committee of Novadaq. JFJ received a research grant from Merck and fees for consulting from Shionogi. RG, CGL, JP, JFJ, LGB, NM, JF, GG, CAV, SRB, and MB have no relevant competing interests to declare.

Word Count

3,205

Table 1 – Schedule of Patient-Reported Outcome Measures

	Preoperatively	1 month	3 months	6 months	12 months
EORTC-QLQ-C30	X	X	X	X	X
MYMOP2		X		X	X
PAM-13	X	X		X	X
LARS Score, WFIS, BQoL		X	X	X	X
HADS	X	X		X	X
Knowledge	X	X		X	
Satisfaction				X	

EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30
MYMOP2 = Measure Your Medical Outcome Profile
PAM-13 = Patient Activation Measure
LARS Score = Low Anterior Resection Syndrome Score
WFIS = Wexner Fecal Incontinence Score
BQoL = Bowel-Related Quality of Life
HADS = Hospital Anxiety and Depression Scale

Table 2 – Characteristics of patient participants in focus group (caregivers not included)

Characteristics	**n = 6**
Age, years, median (range)	61 (32-71)
Gender, n	-
Male	4
Female	2
Neoadjuvant radiotherapy, n	5
Diverting loop ileostomy, n	5
Extent of mesorectal excision, n	-
Partial mesorectal excision	0
Total mesorectal excision	6
Anastomotic height, n	-
Colo-Rectal Anastomosis	3
Colo-Anal Anastomosis	3
Anastomotic leak, n	1
Months since proctectomy, median (range)	15 (7-22)
LARS Score, median (range)	28 (12-39)
LARS Score severity, n	-
Major	3
Minor	2
None	1
Overall, how much does your bowel function affect your QoL?	-
Not at all / very little	2
Somewhat	2
A lot	2
EORTC global quality of life, median (range)	83 (50-100)

QoL = quality of life; EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30

Table 3 – Principal findings from thematic analysis of focus group with patients and caregivers

LARS is as much a psychological disorder as it is a physical condition	Participants felt underprepared for their new bowel function, which greatly contributed to their anxiety
	Participants felt alone and isolated, as if they were the only patients experiencing these symptoms
	Participants were never explained that symptoms may improve; most felt extremely hopeless in the first few months postoperatively
The booklet was easy to read and follow	Participants found that the booklet was written at an appropriate level for patients
	Participants found the images extremely helpful in understanding how, and why, LARS occurs
	Participants felt that the booklet was complete, and was a perfect length
Information was lacking in certain keys areas	Participants wanted more emphasis to be placed on emotional wellbeing in the booklet
	Participants wanted more examples of foods that could trigger their LARS, as well as more detail on how to use and find an enema
	Participants agreed that it is vital to have a dedicated nurse to review the booklet and provide additional support
The booklet is an excellent resource that would have made a big difference in their first year	The booklet's greatest impact is in terms of expectation management and psychological reassurance
	Participants agreed that they would have consulted the booklet frequently in the first year after surgery

LARS: Low Anterior Resection Syndrome

Table 4 – Characteristics of interviewed healthcare professionals

Characteristics	**n = 10**
Gender, n	-
Male	5
Female	5
Practice, n	-
Colorectal Surgeon	7
Nurse	3
Experience, years, median (range)	-
Colorectal Surgeon	16 (9-21)
Nurse	19 (4-22)
Annual rectal cancer volume, patients, median (range)	-
Colorectal Surgeon	30 (20-50)
Nurse	50 (50-75)
Time spent per visit discussing LARS, minutes, median (range)	-
Colorectal Surgeon	8 (5-20)
Nurse	23 (30-45)

Table 5 – Principal findings from thematic analysis of semi-structured interviews with healthcare professionals

Barriers to effectively educating patients on LARS	All HCPs felt that "insufficient time in their schedules" was the most significant barrier to adequately discussing LARS with their patients
	Most HCPs felt that information provided to patients in clinic is often not retained
	Most HCPs did not have a consistent resource on LARS to offer to patients
The booklet is accurate, comprehensive, and easy to read	All HCPs felt that the major points on LARS were covered
	Most HCPs felt that less information on rectal cancer was needed in the booklet
	All HCPs felt that the illustrations were accurate and helpful in explaining LARS
	Several additional medications were recommended (e.g., codeine, amitriptyline)
The booklet is a clinically relevant resource for patients	All HCPs would give this booklet to their patients, and believe that it would a helpful supportive resource
	All HCPs would give it just prior to surgery (or ileostomy closure, if a stoma was performed)

LARS = Low Anterior Resection Syndrome; HCP = healthcare professional

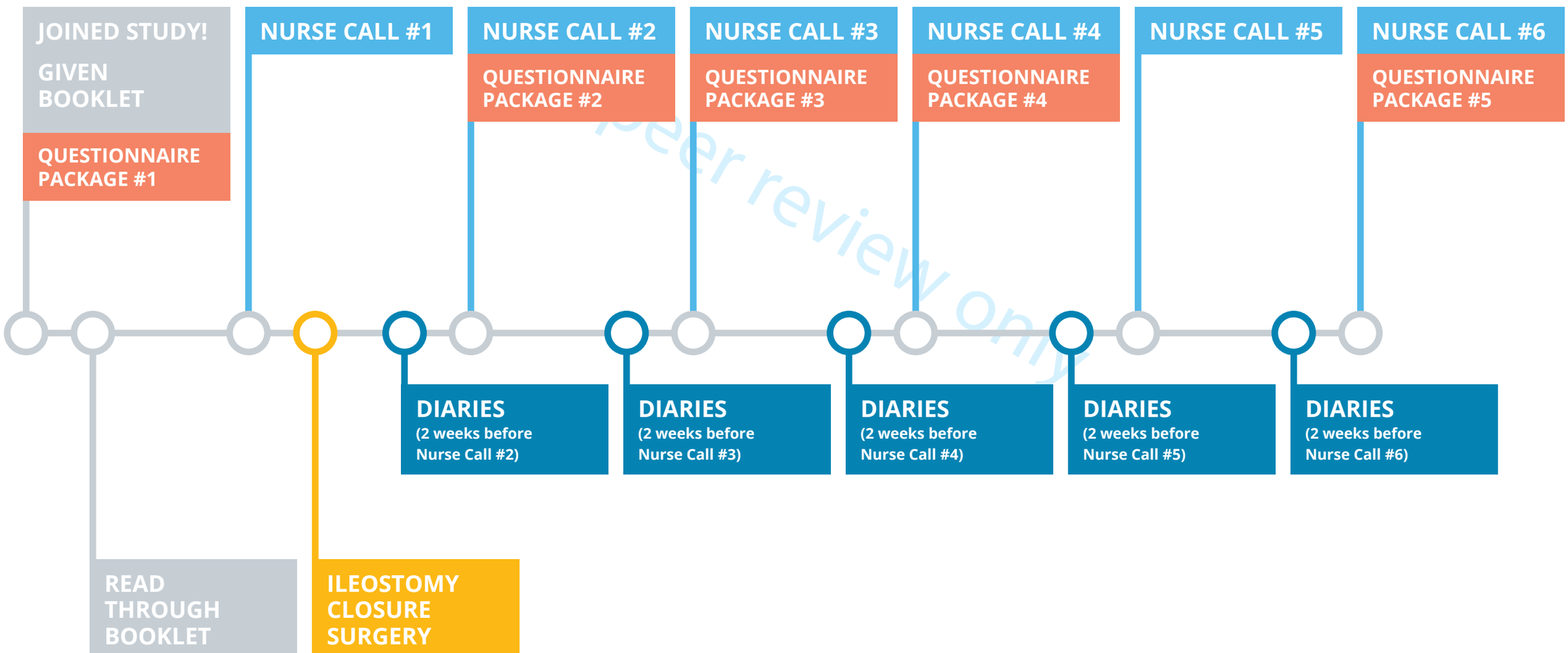
Figures Legend

Figure 1 – Study timeline for patients in the LARS Patient-Centered Program

Figure 2 – Study timeline for patients in the Standard Care Group

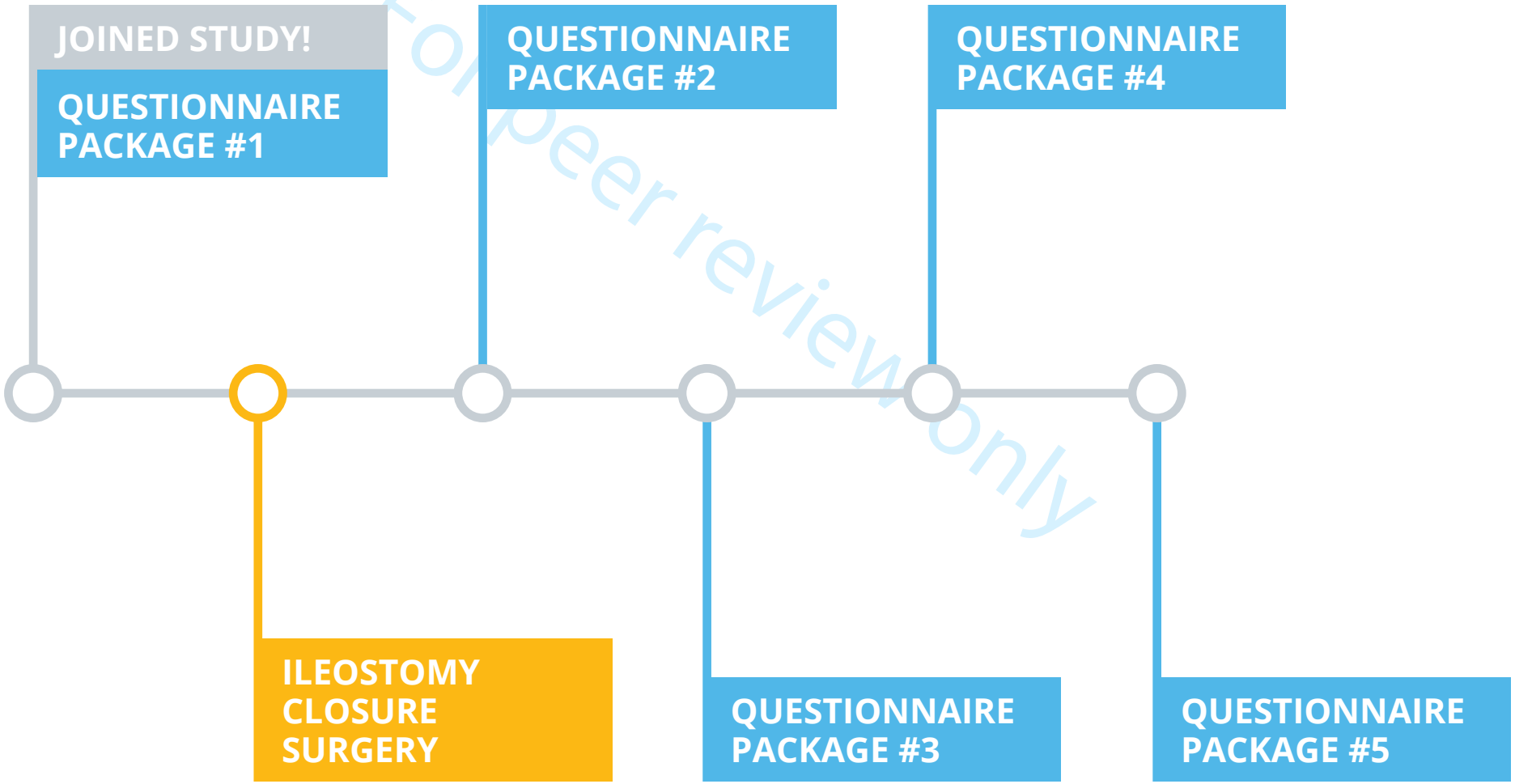
LARS STUDY TIMELINE

LARS Patient-Centered Program



LARS STUDY TIMELINE

Standard Care



SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **Yes – page 1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **Yes – page 3 and 14**
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support **Yes – page 21**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **Yes – page 21**
	5b	Name and contact information for the trial sponsor **Not applicable**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities **Not applicable**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **Yes – pages 5 and 6**

	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses **Yes – page 7**
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **Yes – pages 7, 8 and 9**

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **Yes – page 7**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **Yes – page 7**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **Yes – pages 8, 9 and 10**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **Not applicable**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **Yes – pages 10 and 13**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **Yes – pages 8 and 9**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **Yes – pages 10, 11 and 12**

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) **Yes – Figures 1 and 2**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **Yes – page 13**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **Yes – page 13**

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **Yes – page 7 and 8**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **Yes – page 7 and 8**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **Yes – page 7 and 8**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **Yes – page 10**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **Not applicable**

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **Yes – pages 10, 11 and 12**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **Yes – page 10**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **Yes – page 13**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **Yes – page 13**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **Yes – page 13**
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **Not performed**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **Not applicable**

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **Yes – page 16**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) **Yes – page 16**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **Not applicable**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **Yes – page 21**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators **Yes – page 17**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **Yes – pages 16 and 17**
	31b	Authorship eligibility guidelines and any intended use of professional writers **Not applicable**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **Yes – page 17**

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates **Not applicable**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **Not applicable**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Development and Evaluation of a Patient-Centered Program for Low Anterior Resection Syndrome: Protocol for a Randomized Controlled Trial

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Development and Evaluation of a Patient-Centered Program for Low Anterior Resection Syndrome: Protocol for a Randomized Controlled Trial

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ABSTRACT

Introduction: Low Anterior Resection Syndrome (LARS) is described as disordered bowel function after rectal resection that leads to a detriment in quality of life, and affects the majority of individuals following restorative proctectomy for rectal cancer. The management of LARS includes personalized troubleshooting and effective self-management behaviors. Thus, affected individuals need to be well informed and appropriately engaged in their own LARS management. This manuscript describes the development of a LARS Patient-Centered Program (LPCP) and the study protocol for its evaluation in a randomized controlled trial.

Methods and Analysis: This will be a multicenter, randomized, assessor-blind, parallel-groups, pragmatic trial evaluating the impact of a LPCP, consisting of an informational booklet, patient diaries, and nurse support, on patient-reported outcomes after restorative proctectomy for rectal cancer. The informational booklet was developed by a multidisciplinary LARS team, and was vetted in a focus group and semi-structured interviews involving patients, caregivers, and healthcare professionals. The primary outcome will be global quality of life (QoL), as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (QLQ-C30), at 6 months after surgery. The treatment effect on global QOL will be modeled using generalized estimating equations. Secondary outcomes include patient activation, bowel function measures, emotional distress, knowledge about LARS, and satisfaction with the LPCP.

Ethics and Dissemination: The Research Ethics Committee (REC) at the Integrated Health and Social Services Network (CIUSSS) for West-Central Montreal (health network responsible for the Jewish General Hospital) is the overseeing REC for all Quebec sites. They have granted ethical approval (MP-05-2019-1628) for all Quebec hospitals (Jewish General Hospital, McGill

University Health Center, CHU de Quebec) and have granted full authorization to begin research at the Jewish General Hospital. Patient recruitment will not begin at the other Quebec sites until inter-institutional contracts are finalized and feasibility / authorization for research is granted by their respective REC. The results of this study will be presented at national and international conferences, and a manuscript with results will be submitted for publication in a high-impact peer-reviewed journal.

Registration: This trial was registered on clinicaltrials.gov on February 4, 2019 (no: NCT03828318).

Strengths and Limitations of the Study

- This will be the first randomized controlled trial evaluating a supportive intervention for patients with Low Anterior Resection Syndrome
- This study will collect longitudinal data on patient-reported outcomes following restorative proctectomy, and will report on the natural evolution of several important outcome measures over the first postoperative year
- The informational booklet used in the trial underwent a rigorous pre-trial assessment and was revised into its final format based on feedback obtained in focus groups involving patients, caregivers, and healthcare professionals
- As with any longitudinal study, there is a risk for attrition throughout the study period, which could be a source of bias in the final results
- Management in the standard care group will vary by institution; however, none of the participating institutions have a formal LARS program for rectal cancer survivors

INTRODUCTION

Restorative proctectomy is increasingly performed for rectal cancer as surgeons continue to push the limits of sphincter preservation.[1,2] However, despite avoiding a permanent ostomy, many individuals are left with significant bowel dysfunction after sphincter-sparing surgery. Low Anterior Resection Syndrome (LARS) encompasses a series of negative bowel symptoms, such as frequency, urgency, incontinence, and clustering of bowel movements,[3] that can affect 70 to 90% of patients following restorative proctectomy.[4,5] Although symptoms may improve somewhat in the first year or two after surgery, long-term bowel dysfunction often remains in more than 70% of patients and major dysfunction in over 50%.[6-8] As such, LARS remains a significant concern for rectal cancer survivors and their significant others, as increased severity correlates with worse perceived global health status and quality of life (QoL).[5,8,9]

Currently, there is no well-established treatment strategy for LARS, and management is both empirical and symptom-based.[4] LARS is usually managed with a combination of lifestyle, pharmacological, and at times, interventional strategies, with mixed success. Due to the individual nature of each patient's cluster of symptoms, much of the care requires personalized troubleshooting and self-management behaviors to improve bowel symptoms and QoL.[4] These behaviors include understanding one's own symptoms, knowing how to use and dose stool bulking agents and anti-diarrheal medications, performing pelvic floor exercises, adhering to dietary recommendations, proper perianal skin management, and preparing ahead of social engagements. Thus, individuals need to be well informed, motivated and engaged in their own LARS management to take more control over their bowel function and achieve optimal outcomes.

Among individuals undergoing rectal resection with a permanent ostomy (e.g., abdominoperineal resection), there is evidence that supportive and informational interventions improve QoL, ostomy proficiency, self-efficacy and knowledge.[10-12] However, evidence regarding the impact of such interventions in patients who undergo restorative proctectomy is lacking, despite the latter operation being far more frequently performed.[1] When provided with the means to better understand and control important aspects of their bowel function, patients may be more likely to experience positive improvements in self-reported outcomes. In a recent review comparing long-term patient-reported outcomes after ostomy or sphincter-sparing surgery for low rectal cancer, the authors concluded that interventions geared towards patients without ostomies warrant further attention.[13]

This paper describes a study protocol for a randomized controlled trial (RCT) investigating the impact of a LARS Patient-Centered Program (LPCP) on patient-reported outcomes after restorative proctectomy for rectal cancer. Furthermore, qualitative data are presented that were gathered through a focus group assembling individuals with LARS and their caregivers, and through semi-structured interviews with rectal cancer healthcare professionals, as a joint effort to develop the LPCP.

METHODS AND ANALYSIS

Phase 1: Study Protocol for Proposed RCT

The study protocol was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.[14]

Objectives

The overall objective of this study is to evaluate the effects of a LPCP on patient-reported outcome measures (PROMs) after restorative proctectomy for rectal cancer. Specifically, our primary objective is to evaluate the extent to which a LPCP improves global QoL, as measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core 30 (QLQ-C30), at 6 months after surgery in comparison to standard care. Secondary objectives include the effects of a LPCP on symptom change, patient activation, bowel function, emotional distress, patient knowledge, and satisfaction with LARS care.

Participants and Setting

This multicenter RCT involves participants from multiple institutions across North America with high-volume Colorectal Surgery or Surgical Oncology practices. Patients who have undergone restorative proctectomy for neoplastic disease (benign or malignant) located in the rectum (0-15cm from the anal verge) with a diverting ostomy and who are scheduled for ostomy closure are eligible for inclusion. Patients will be recruited approximately one month prior to ostomy closure by their individual surgeon, who will go through the informed consent process with them. Exclusion criteria include: 1) active chemotherapy or radiotherapy treatment at the time of consent; 2) major colonic resection in addition to proctectomy; 3) inability to be contacted by telephone; 4) inability to read and comprehend English or French; and 5) inability to provide clear and informed consent. The study is estimated to be open from November 2019 to November 2022.

Randomization

Consecutive participants will be randomized in a 1:1 ratio into one of two groups: 1) LARS Patient-Centered Program; or 2) Standard Care. Block randomization with randomly varying block sizes will be performed to ensure an equal number of participants in each group.

Randomization will also be stratified by participating institution. An online centralized computer-generated randomization sequence will be used to ensure allocation concealment.

LARS Patient-Centered Program

The LPCP consists of an informational booklet, patient diaries, and nursing support made available only to patients randomized to the intervention group.

1. Informational Booklet and Patient Diaries:

The goals of the booklet are to inform individuals with rectal cancer about postoperative bowel dysfunction, manage expectations, and review the different treatment strategies. Prior to developing the booklet, our team conducted a systematic review of online health information for LARS to assess the readability, suitability, quality, accuracy and content of materials currently available to patients.[15] We concluded that the current body of health information for patients with LARS is suboptimal. In particular, no patient material was written at the American Medical Association-recommended 6th grade reading level, there was little use of headings, summaries and illustrations to accompany the text, and important content was missing. We then set out to develop our own informational booklet, drawing on the important elements emphasized in each assessment tool used in the systematic review. After developing the first draft of the booklet, patients, caregivers, and healthcare professionals provided feedback to improve the booklet into its current format. The booklet was then translated into French and underwent a similar evaluation process. A more thorough description of the booklet's development process can be found below (see Phase 2 below).

The booklet will be introduced to patients at the time of study recruitment (before ostomy closure). Participants will be instructed to read through the booklet at least once prior to their ostomy closure operation and will be encouraged to consult it as much as needed thereafter. In

addition to the informational booklet, participants will receive Bowel Symptom, Diet, and Loperamide diaries and will be instructed to use them whenever experiencing any symptoms of bowel dysfunction, and for 2 weeks prior to each scheduled nurse phone call (please see the next section below). The goal of these diaries is to assist participants in recognizing the underlying patterns related to their symptoms so that they can optimize their self-management.

2. Nursing Support:

Nursing support will be centralized from one institution and made available to participants in the intervention group, by telephone and email. The study nurse (bilingual in English and French) has expertise in rectal cancer management and postoperative bowel dysfunction. She will briefly review the booklet content with participants by telephone at the beginning of the study (prior to ostomy closure) and answer related questions. Postoperatively, the nurse will have scheduled telephone calls with participants at 1-, 3-, 6-, 9-, and 12-months, to provide support and periodically review their completed diaries for troubleshooting. Lastly, she will be available to speak with participants in between scheduled calls, either by phone or by email.

Standard Care Group

Participants randomized to the standard care group will not have access to either the informational booklet nor nursing support. Instead, they will only receive a paper copy (and/or instructions for online access) of the Colorectal Cancer Association of Canada (CCAC) module on "Living with Colorectal Cancer". The standard care group will also receive the usual care for LARS information and counseling that is routinely made available at their hospital, with participating hospitals asked to provide a description of what constitutes "standard care" for LARS. Due to the expected heterogeneity in institutional LARS practices, participating

institutions will be accounted for in the final statistical model in addition to stratified randomization by institution. Participants in the standard care group will be told that they can have access to the informational booklet when the study is complete.

Data Collection

Baseline demographics, medical comorbidities, and disease and treatment characteristics will be obtained from chart review, including known predictors of bowel dysfunction (e.g., tumor height, neoadjuvant radiotherapy, type of proctectomy [total vs. partial mesorectal excision], reconstruction technique [straight anastomosis vs. neorectal reservoir], and anastomotic leak after proctectomy). The remaining data will be gathered from self-reported questionnaires at study time-points throughout the 12-month study period.

Outcomes

Outcomes will be measured with the use of various PROMs and recorded into an online registry (REDCap) by a blinded assessor. PROMs captured at the same time-point will be completed as a single package. The schedule for all PROMs can be found in Table 1. The PROM package for each time-point (available in both English and French) will either be mailed to participants, disseminated via email, or completed over the phone, depending on participants' preferences. Participants will receive email and telephone reminders for incomplete questionnaires. The study timeline for both groups can be found in Figures 1 and 2. The following outcomes and PROMs will be collected:

1. Quality of Life:

QoL will be measured using the EORTC-QLQ-C30, a self-report questionnaire developed to assess QoL for patients living with or beyond cancer. It consists of 30 items, which aggregate into 1 global QoL scale, 5 functional scales, 3 symptom scales, and 6 single items. The

EORTC-QLQ-C30 has been well validated in individuals with rectal cancer and correlates significantly with LARS severity.[5,8,9]

2. Symptom Changes:

The Measure Your Medical Outcome Profile (MYMOP2) is a patient-centered measure that assesses changes over time in a specific symptom identified as most bothersome to the patient.[16,17] The patient also identifies a daily activity that is being restricted or prevented by the symptom. Both the symptom and the activity are scored using a 6-point Likert-type scale in the last week.

3. Patient Activation:

Patient activation measures the degree of knowledge, skills, and confidence for self-management of healthcare.[18] In patients with chronic medical conditions, patient activation is associated with increased adherence to medication and decreased healthcare resource utilization.[19] We believe that the LPCP may increase patient activation, which may ultimately translate into increased patient engagement in their LARS healthcare.

The Patient Activation Measure-13 (PAM-13) is a 13-item questionnaire. Responses are based on a Likert scale ranging from “disagree strongly” to “agree strongly”, and the final score is a transformation ranging from 0 to 100 according to a conversion formula provided by the developers. Activation is then categorized into 1 of 4 groups based on their transformed score: Level 1, “overwhelmed and not ready to take an active role” (≤47.0); Level 2, “realize they have a role to play, but lack the knowledge and confidence” (47.1-55.1); Level 3, “beginning to take action, but still lack confidence” (55.2-72.4); Level 4, “can manage their healthcare, but may struggle to maintain the behaviors” (≥72.5).

4. Bowel Function:

Bowel function will be measured postoperatively using three validated tools/questions. The LARS Score is a 5-item tool aimed at symptoms of bowel dysfunction, with each question weighted differently according to the perceived importance by patients. The scores of the 5 questions sum to 42 points. The LARS Score allows the categorization of patients as having major (30-42 points), minor (21-29 points), or no LARS (0-20 points). The Cleveland Clinic Florida / Wexner Fecal Incontinence Score (WFIS) is a 5-item tool aimed at measuring the frequency of incontinence to gas and liquid or solid stools, and its consequences (pad wearing and lifestyle alterations). Each question ranges from 0 (never) to 4 (always) and the total score is measured out of 20. Lastly, each participant will be asked a single, validated, bowel-related QoL question: "Overall, how much does your bowel function affect your quality of life?" Responses categorize respondents into 1 of 3 grades: "not at all" (no impairment); "very little" (minor impairment); "somewhat" or "a lot" (major impairment). Bowel-related QoL is significantly correlated with both the LARS Score and general QoL as per previous studies.[9]

5. Emotional Distress:

Many patients with LARS describe emotional distress, anxiety, and isolation (see Phase 2 below). The LPCP is designed to alleviate some of the distress associated with LARS, and may provide hope that symptoms can be optimally managed.

Emotional distress will be measured using the Hospital Anxiety and Depression Scale (HADS), which has been validated in colorectal cancer survivors.[20,21] It includes 7 items aimed at assessing depression and 7 items for anxiety. Each item is scored 0-3, and is based on frequency of symptoms. The total score is out of 21, and individuals can be categorized as "normal" (0-7), "borderline abnormal" (8-10), or "abnormal" i.e., depressed or anxious (11-21).

6. Knowledge:

Given that the LPCP is partly an informational intervention, knowledge related to LARS will be measured using a short, investigator-generated, multiple-choice questionnaire. The items reflect key concepts in etiology/risk factors and management of LARS. We believe that improving LARS knowledge will further improve patient activation and engagement in LARS healthcare, which may lead to improvements in QoL and possibly bowel function.

7. Satisfaction:

Satisfaction related to LARS care received throughout the study period (information and support) will be assessed in both groups using a short, investigator-generated, 2-item questionnaire. Responses will be recorded using a 5-point Likert scale, ranging from "not satisfied" (1) to "very satisfied" (5).

Statistical Analysis

Descriptive analyses will include means with standard deviations, medians with ranges, or frequencies with proportions, where appropriate. Continuous outcomes will be compared using a t-test or Wilcoxon rank-sum test and categorical outcomes using χ^2 tests. The treatment effect on global QoL and bowel function will be modeled using generalized estimating equations (GEE).[22] This method accounts for 1) the within-subject correlation between responses at different time-points, and 2) possible clustering of responses among patients from the same hospital. GEE models also make use of all the available data, so that patients can contribute to the model if they have data available for any single time-point. An appropriate correlation structure will be chosen using the quasi-likelihood information criterion. The effect size, standard error, and 95% confidence interval for the estimate of the treatment effect at 6 months

will be reported. For the remaining secondary outcomes, pairwise comparisons will be performed at various time-points.

Power Analysis and Sample Size Calculations

The primary outcome of the study is global QoL at 6 months, as measured by the EORTC QLQ-C30. Based on the largest available cohort of patients with QoL data who have undergone restorative proctectomy for rectal cancer and who are ostomy-free, mean global QoL score is assumed to be 77 (maximum possible score is 100) with a standard deviation of 19.[9] According to the consensus guidelines on the use of the EORTC QLQ-C30 to power a randomized controlled trial, a mean difference in global QoL of 10 points (small-medium treatment effect) is the most appropriate expected effect-size for interventions aimed to improve QoL in cancer patients.[23] Thus, with an alpha=0.05 and power=0.80, we estimate that 45 participants are required in each arm of our study. Given the risk for attrition over the 6-month study period, the adjusted final sample size accounting for a 30% attrition rate is 64 participants in each arm (128 patients in total).

Registration

This trial was registered on clinicaltrials.gov on February 4, 2019 (no: NCT03828318).

Phase 2: Development of Informational Booklet

The first draft of the informational booklet was developed by a multidisciplinary team of healthcare professionals who care for patients with rectal cancer. The initiative was co-led by a General Surgery resident (R.G.) and a Colorectal Surgery attending (M.B.), and included a senior colorectal cancer oncology pivot nurse, pelvic physiotherapist, and members of the McGill University Patient Education Office. The booklet was designed to review important information

regarding the epidemiology, symptomatology, and management of LARS. The booklet was written at a 6th-grade reading level, which is recommended by the American Medical Association for any patient material,[24] and included original illustrations designed by our team.

An Institutional Review Board-approved qualitative study was subsequently undertaken to evaluate the booklet. A single focus group with rectal cancer patients and their caregivers, as well as individual semi-structured telephone interviews with healthcare professionals, were conducted.

Participants for the focus group were recruited from individual Colorectal Surgeons practicing at a single institution. The focus group included 12 participants (six patients and their caregivers/partners) and followed a semi-structured interview guide (Supplementary File 1). Each patient was a minimum of 6-months removed from ileostomy closure (if diverted) or proctectomy. Participants' characteristics are reported in Table 2. Each participant/caregiver was given two copies of the informational booklet and allowed three weeks to review the booklet and generate their own thoughts. The purpose of the focus group was to obtain feedback regarding the first draft of the booklet, to better understand participants' current/past experiences with LARS, and to incorporate changes into the booklet to meet the informational needs of rectal cancer survivors. The focus group was audio-recorded and transcribed, and data were analyzed using the grounded theory.[25,26] The constant comparative method was applied; data from participants were coded based on emerging patterns, concepts, and themes to generate theory, which was then analyzed and categorized accordingly so that descriptive statements could be formed.[27] The principal findings from the thematic analysis of the focus group are displayed in Table 3. Patients and their caregivers described the emotional difficulties of living with LARS and the general lack of support and preparation they received from their healthcare team. They

unanimously supported the development and dissemination of the booklet, reporting that it would have had a major impact on their outlook and knowledge regarding LARS in their first year after surgery. Some of the feedback included more emphasis to be placed on expectation management and emotional support, and they asked for more detail regarding enema use. They also requested a list of healthcare providers who could support them in their LARS care, and more examples for foods which may activate their LARS.

Healthcare professionals from multiple institutions across North America were invited to review the booklet as well. In total, 10 healthcare professionals comprised of seven Colorectal Surgeons and three nurses in Gastrointestinal Oncology, and each was interviewed using a semi-structured interview guide (Supplementary File 2). Characteristics of the healthcare professionals are reported in Table 4. Similar to patient participants, each healthcare professional was given one copy of the informational booklet and allowed three weeks to review the booklet and generate their own thoughts. The focus of these interviews was largely on content and management strategies; to ensure that our booklet would be as comprehensive and inclusive as possible. Furthermore, healthcare professionals were asked about the layout and structure, clinical applicability, and other means of improving the booklet. Similar to the focus group, the interviews were recorded, and the same methods were used for data analysis. The principal findings from the interviews are displayed in Table 5. Healthcare professionals felt that the booklet was accurate and comprehensive, and that it would complement the role of a clinician/nurse in supporting patients with LARS. Several interviewees recommended additional medications and illustrations, but did not feel the layout or structure needed to be further revised. Small changes in language were recommended as well (e.g., “stoma” instead of “bag” – most healthcare professionals felt that patients understand the meaning of stoma).

Based on the results of this qualitative study, the informational booklet was modified into its final format. The booklet was then professionally translated into French language, and underwent a similar evaluation process with French-speaking patient volunteers.

Patient and Public Involvement

Patients were involved in the development of the informational booklet to be used as part of the LPCP. Patients and the public were not involved in the design of the study; however, the outcomes proposed in this study are specifically designed to assess participants' experience with LARS and the LPCP. The authors would also like to thank Dr.'s Steven D. Wexner, Patricia Sylla, Mitchell Bernstein, as well as Holly Bonnette and Tracy Chornopyski, for their contributions.

Ethics and Dissemination

The Research Ethics Committee (REC) at the Integrated Health and Social Services Network (CIUSSS) for West-Central Montreal (health network responsible for the Jewish General Hospital) is the overseeing REC for all Quebec sites. They have granted ethical approval (MP-05-2019-1628) for all Quebec hospitals (Jewish General Hospital, McGill University Health Center, CHU de Quebec) and have granted full authorization to begin research at the Jewish General Hospital. Patient recruitment will not begin at the other Quebec sites until inter-institutional contracts are finalized and feasibility / authorization for research is granted by their respective REC. The English-language patient consent is presented as Supplementary File 3.

The results of this study will be presented at national and international meetings, and a manuscript will be submitted for publication in a high-impact peer-reviewed journal. We

anticipate that the findings will inform the development of future rectal cancer survivorship programs with a focus on bowel dysfunction, in an effort to improve the long-term QoL of individuals with rectal cancer.

Data Sharing Statement

Individual patient data from this trial will not be shared.

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Author Contributions

RG, CGL, JP, JFJ, LGB, ASL, NM, JF, GG, CAV, SRB, and MB contributed to the design of the study. RG, CGL, JP, LGB, ASL, NM, JF, GG, CAV, and MB participated in qualitative data acquisition. RG, CGL, JFJ, SRB, and MB contributed to the data analysis plan. RG, JP, LGB, ASL, NM, JF, GG, CAV, and MB were involved in obtaining ethical approval. RG and MB prepared the first draft of the manuscript. RG, CGL, JP, JFJ, LGB, ASL, NM, JF, GG, CAV, SRB, and MB contributed to, and approved, the final version of the manuscript.

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Competing Interests Statement

ASL receives travel stipends from Merck and Servier, and is on the advisory committee of Novadaq. JFJ received a research grant from Merck and fees for consulting from Shionogi. RG, CGL, JP, JFJ, LGB, NM, JF, GG, CAV, SRB, and MB have no relevant competing interests to declare.

Word Count

3,205

Table 1 – Schedule of Patient-Reported Outcome Measures

	Preoperatively	1 month	3 months	6 months	12 months
EORTC-QLQ-C30	X	X	X	X	X
MYMOP2		X		X	X
PAM-13	X	X		X	X
LARS Score, WFIS, BQoL		X	X	X	X
HADS	X	X		X	X
Knowledge	X	X		X	
Satisfaction				X	

EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30
MYMOP2 = Measure Your Medical Outcome Profile
PAM-13 = Patient Activation Measure
LARS Score = Low Anterior Resection Syndrome Score
WFIS = Wexner Fecal Incontinence Score
BQoL = Bowel-Related Quality of Life
HADS = Hospital Anxiety and Depression Scale

Table 2 – Characteristics of patient participants in focus group (caregivers not included)

Characteristics	**n = 6**
Age, years, median (range)	61 (32-71)
Gender, n	-
Male	4
Female	2
Neoadjuvant radiotherapy, n	5
Diverting loop ileostomy, n	5
Extent of mesorectal excision, n	-
Partial mesorectal excision	0
Total mesorectal excision	6
Anastomotic height, n	-
Colo-Rectal Anastomosis	3
Colo-Anal Anastomosis	3
Anastomotic leak, n	1
Months since proctectomy, median (range)	15 (7-22)
LARS Score, median (range)	28 (12-39)
LARS Score severity, n	-
Major	3
Minor	2
None	1
Overall, how much does your bowel function affect your QoL?	-
Not at all / very little	2
Somewhat	2
A lot	2
EORTC global quality of life, median (range)	83 (50-100)

QoL = quality of life; EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30

Table 3 – Principal findings from thematic analysis of focus group with patients and caregivers

LARS is as much a psychological disorder as it is a physical condition	Participants felt underprepared for their new bowel function, which greatly contributed to their anxiety
	Participants felt alone and isolated, as if they were the only patients experiencing these symptoms
	Participants were never explained that symptoms may improve; most felt extremely hopeless in the first few months postoperatively
The booklet was easy to read and follow	Participants found that the booklet was written at an appropriate level for patients
	Participants found the images extremely helpful in understanding how, and why, LARS occurs
	Participants felt that the booklet was complete, and was a perfect length
Information was lacking in certain keys areas	Participants wanted more emphasis to be placed on emotional wellbeing in the booklet
	Participants wanted more examples of foods that could trigger their LARS, as well as more detail on how to use and find an enema
	Participants agreed that it is vital to have a dedicated nurse to review the booklet and provide additional support
The booklet is an excellent resource that would have made a big difference in their first year	The booklet's greatest impact is in terms of expectation management and psychological reassurance
	Participants agreed that they would have consulted the booklet frequently in the first year after surgery

LARS: Low Anterior Resection Syndrome

Table 4 – Characteristics of interviewed healthcare professionals

Characteristics	**n = 10**
Gender, n	-
Male	5
Female	5
Practice, n	-
Colorectal Surgeon	7
Nurse	3
Experience, years, median (range)	-
Colorectal Surgeon	16 (9-21)
Nurse	19 (4-22)
Annual rectal cancer volume, patients, median (range)	-
Colorectal Surgeon	30 (20-50)
Nurse	50 (50-75)
Time spent per visit discussing LARS, minutes, median (range)	-
Colorectal Surgeon	8 (5-20)
Nurse	23 (30-45)

Table 5 – Principal findings from thematic analysis of semi-structured interviews with healthcare professionals

Barriers to effectively educating patients on LARS	All HCPs felt that "insufficient time in their schedules" was the most significant barrier to adequately discussing LARS with their patients
	Most HCPs felt that information provided to patients in clinic is often not retained
	Most HCPs did not have a consistent resource on LARS to offer to patients
The booklet is accurate, comprehensive, and easy to read	All HCPs felt that the major points on LARS were covered
	Most HCPs felt that less information on rectal cancer was needed in the booklet
	All HCPs felt that the illustrations were accurate and helpful in explaining LARS
	Several additional medications were recommended (e.g., codeine, amitriptyline)
The booklet is a clinically relevant resource for patients	All HCPs would give this booklet to their patients, and believe that it would a helpful supportive resource
	All HCPs would give it just prior to surgery (or ileostomy closure, if a stoma was performed)

LARS = Low Anterior Resection Syndrome; HCP = healthcare professional

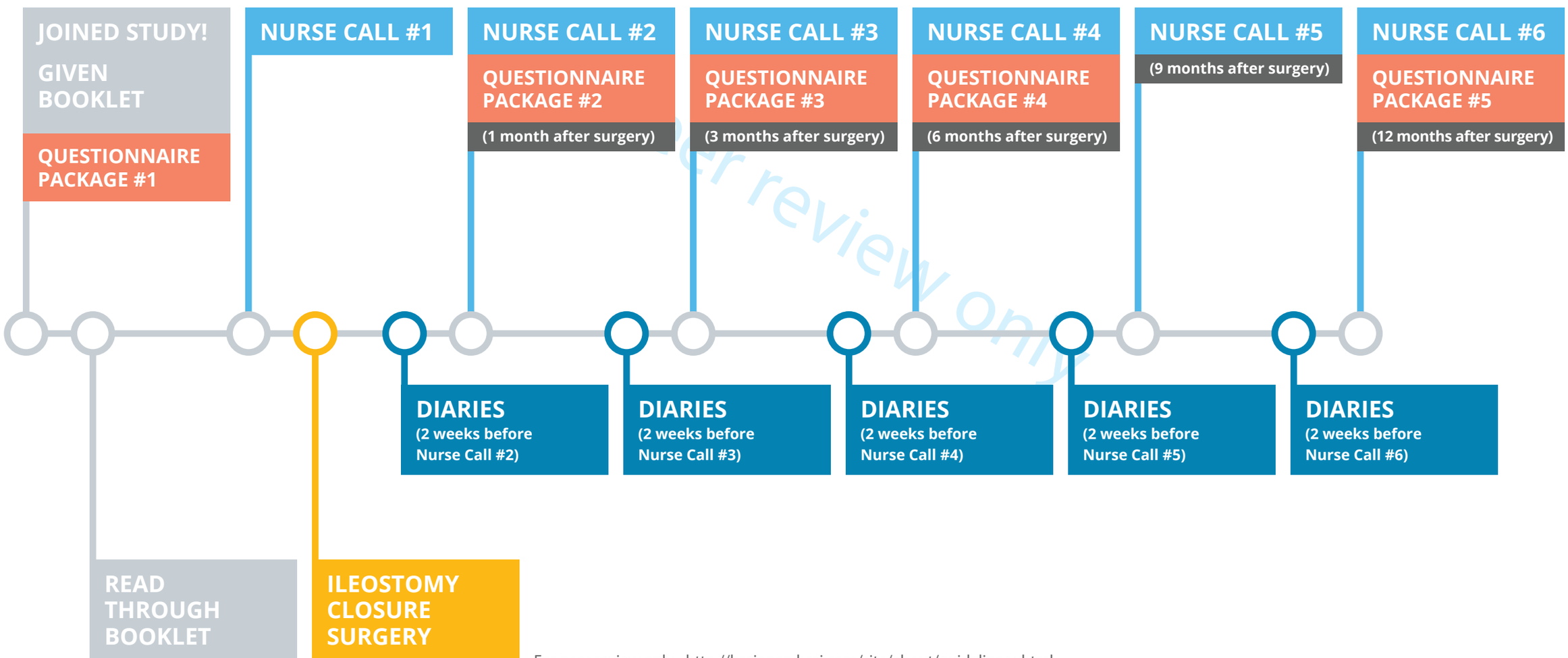
Figures Legend

Figure 1 – Study timeline for patients in the LARS Patient-Centered Program

Figure 2 – Study timeline for patients in the Standard Care Group

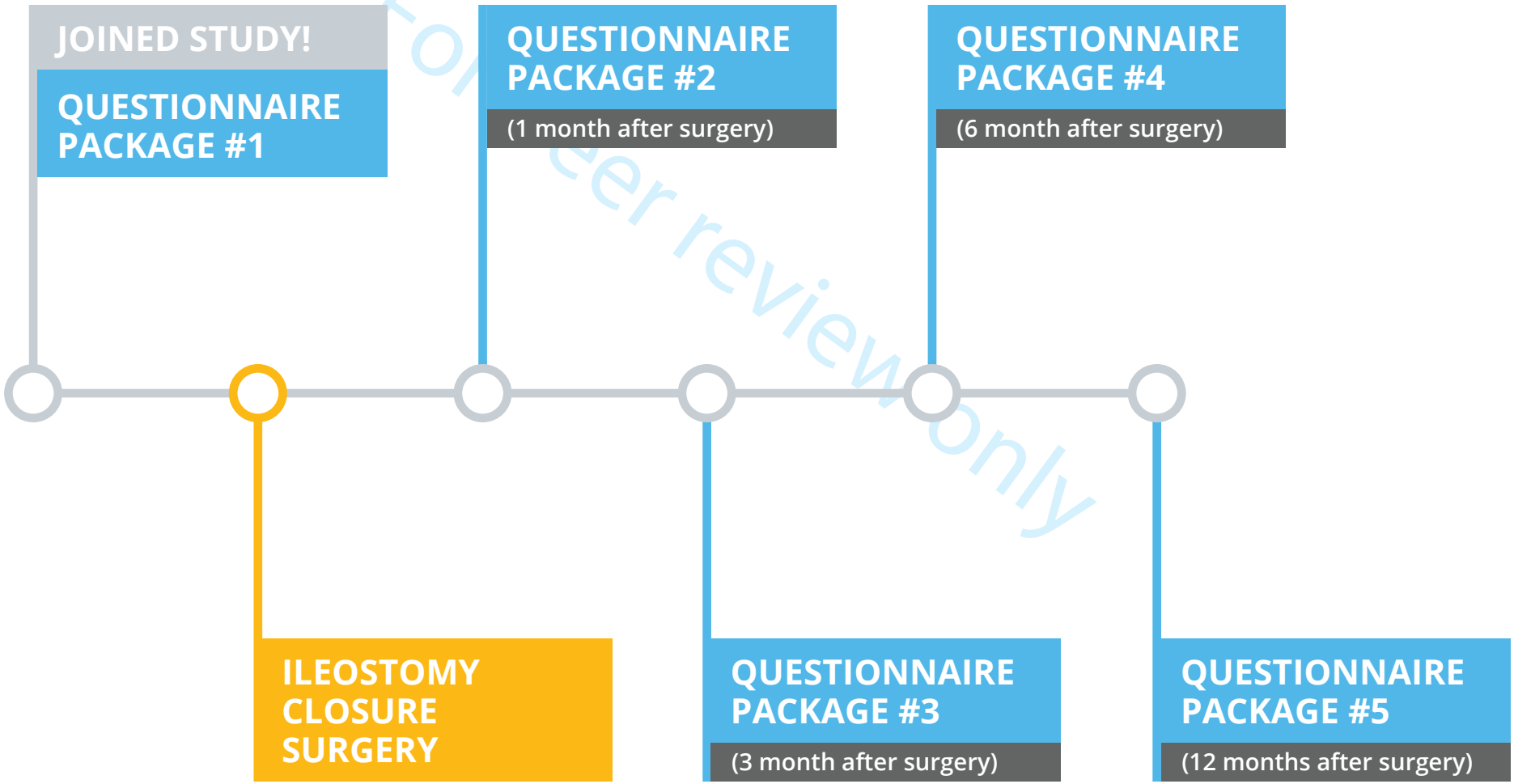
LARS STUDY TIMELINE

LARS Patient-Centered Program



LARS STUDY TIMELINE

Standard Care



Supplementary File 1 – Semi-structured interview guide for focus group with patients and caregivers

Introduction

Good afternoon everybody and welcome! Thank you for being here today and for helping us in the creation of our educational booklet on Low Anterior Resection Syndrome, also know as LARS.

Today I will be asking you about your impressions and feedback of the booklet.

My name is Richard Garfinkle – I am a senior resident in General Surgery and have been conducting research with the Colorectal Surgery group for many years.

You were all invited because you've all undergone surgery for rectal cancer and have been identified by your doctors as having experience with bowel dysfunction since your operation. Your doctors also thought you'd be great participants for this focus group, and we appreciate your input.

There are no wrong answers but rather differing points of view.

Please feel free to share your point of view even if it differs from what others have said. Keep in mind that we're just as interested in negative comments as positive comments, and at times the negative comments are the most helpful.

You've probably noticed the microphone. We're tape recording the session because we don't want to miss any of your comments. People often say very helpful things in these discussions and we can't write fast enough to get them all down. We will be on a first name basis today but we won't use any names in our reports. You may be assured of complete confidentiality.

To respect each other's confidentiality, what has been said here will stay here. Is everyone comfortable with that?

In respect of everyone's time, we will try to wrap this up in under an hour. We may go a little over, but not more than 15 minutes. Is everyone okay with that? If you have to leave at any point, not a problem, just let me know when.

Well, let's begin. We've placed name cards on the table in front of you to help us remember each other's names. Let's find out some more about each other by going around the table. Everyone can introduce themselves by name, and in one or two sentences, describe your story with rectal cancer and your treatment.

Given everyone a chance to speak.
Then proceed with the following:

Now that everyone has been introduced, we can go on with discussing the LARS booklet.

General overview

Overall what is your impression of the booklet?
Who had heard about LARS before reading this booklet, and how / from where?
Was LARS or bowel function after surgery discussed with your surgeon?
What did you like about the booklet?
What did you not like about the booklet?
Have you read or found similar booklets like this one in the past, and where did you find them?

Content

Did you like the information that was chosen for the booklet?
Was there any topic about LARS that was discussed in too much detail?
Was there any topic about LARS that was discussed in too little detail, or not discussed at all?
How was the overall length of the booklet?
In your experience dealing with LARS, have you learnt any tips and tricks that should be added to the booklet?
Are there important abdominal or bowel symptoms that you've had to deal with that are missing from this booklet?
What new information did you learn from this booklet?
For the caregivers in the room: how can the booklet be made better for caregivers to learn about LARS?

Clinical relevance

Would you have liked to receive a booklet like this before your rectal cancer operation?
How would this booklet have better prepared you for life after surgery?
Would you like an Internet (online) or mobile-application version of the booklet?
Do you see yourself reading over this booklet only before surgery, or would you use it again after surgery?

LARS diaries

Have you used bowel or food diaries before? And who suggested you use one?
How did using a diary help you?
What are your thoughts about the diaries that we've included in the booklet?
Would you use these diaries? And how often?
Would you prefer the diary as an online diary or as an app?
How would you improve the diaries?

Final comments

Do you have any final comments?

We've come to the end. Thank you everyone for your time and feedback! It is really appreciated and the past hour or so has been very productive. If anyone has any concerns or anything they want taken out of the recording, let me know, it's not a problem. I'll stick around after to talk if you have anything to say.

Supplementary File 2 – Semi-structured interview guide for healthcare professionals

Introduction

Thank you for agreeing to be part of this study exploring the educational needs of rectal cancer survivors with Low Anterior Resection Syndrome (or LARS). You've been given our educational booklet that we created for patients to use as part of an intervention in a randomized controlled trial, and have agreed to participate in a brief phone interview.

The phone interview will take about 20 minutes. Is now a good time?

Thank you for reading through our first draft of the educational booklet. To ensure that the booklet is relevant and that the content is both accurate and helpful, we appreciate your feedback. This will allow us to improve the booklet prior to giving it to patients.

Participant demographics

What is your full name, role, and institution of work?
How many years have you been in your role?
What volume of rectal cancer patients do you treat a year?
How much time do you currently spend per rectal cancer patient discussing LARS?
What are the barriers to spending more time with patients on this subject?

General overview

What was your overall impression of the booklet?
What are your thoughts regarding the layout and structure of the booklet?
Does the order of topics make sense?
What are your thoughts regarding the images and illustrations selected?
What was your favorite part / least favorite part of the booklet?

Content

Did you notice any inaccurate statements in the booklet?
Is there any important aspect of LARS that is missing from the booklet?
Are there any topics that are explored in too much / too little detail?
Do you have any additional tips and tricks regarding LARS treatment that are not included in the booklet?
Did you learn anything new?

Clinical relevance

Do you think this booklet would be useful for patients?
Would you recommend this booklet to patients and to colleagues?
How can the booklet be made more relevant for patients to use?
Do you think patients would like an online or mobile-application platform for the booklet?

If this booklet is found to be beneficial for patients, how would you incorporate this booklet into clinical practice in the future?

LARS diaries

Do you find the diaries useful for patients?
Have you ever instructed patients to use a bowel or food diary, and what has been their compliance?
What important information is missing from the diaries that might be helpful for patients to better reflect on their bowel symptoms?

Final comments

Do you have any final comments?

We thank you very much for your participation in this interview. Your feedback is greatly appreciated and will help us refine this booklet for the betterment of patient education.

Supplementary File 3 – Patient consent form

Introduction:

You are being invited to be a research participant. This research is designed to investigate the use of a supportive intervention on patient-reported outcomes in patients who have undergone surgery for rectal cancer. You have the right to know about the purpose and procedures that are to be used in this research study, and to be informed about the potential benefits and risks of this research.

Before you agree to take part in this study, it is important that you read the information in this consent form. You should ask as many questions as you need to in order to understand what you will be asked to do. You do not have to take part in this study if you do not want to.

The Medical/Biomedical (MBM) Research Ethics Committee of the Centre intégré universitaire de santé et de services sociaux of West Central Montreal Health (CIUSSS WCMH) has approved and is responsible for the continuing ethical oversight of the study at the Jewish General Hospital.

Goals and Objectives:

After surgery for rectal cancer, many patients suffer from Low Anterior Resection Syndrome (LARS), which includes a variety of negative bowel-related symptoms as a consequence of removing the rectum. LARS can negatively impact quality of life. **The goal of this study is to evaluate the impact of a supportive intervention for LARS, with the hopes that it will improve various outcomes in patient care after surgery.** Specifically, to identify whether our supportive intervention focusing on LARS can:

- improve the quality of life among patients undergoing surgery for rectal cancer
- increase patient engagement in their own healthcare, as measured by the "Patient Activation Measure" (a questionnaire designed at evaluating the patient's knowledge, skills, and confidence in care for their own health)
- improve bowel symptoms
- decrease emotional distress

Procedures:

- We are inviting all patients who underwent a Low Anterior Resection to remove a tumor in the rectum and who had a temporary ostomy ("bag"), and who are now scheduled to have their ostomy closure operation (the "reconnection" operation).
- As part of the study, we will access your medical chart from the hospital and collect some important information regarding your rectal cancer operation, as part of the research.
- You will then be randomly assigned to either the supportive intervention group or the control group (no supportive intervention), meaning that you will have a 50/50 chance of receiving the LARS education
- The **supportive intervention group** will receive two resources to help them manage their LARS:
  1) Educational booklet

2) Specialized nursing care

- The **control group** will **not** have access to the two resources listed above. That does not mean that control group participants shouldn't be counseled on LARS. These participants will have access to any resources that are normally available at their hospital. This may include discussions with their colorectal surgeon in the office, appointments with a nurse, and any pamphlets or online resources that your doctor might normally recommend.

Participants in the intervention group

Educational Booklet

- Participants in the intervention group will have access to an educational booklet.
- This educational booklet offers all of the essential information on LARS, including tips and tricks on how to best manage LARS at home.
- It also offers special diaries for various aspects of treatment, where participants can be expected to write down different things that did, or did not, work for their LARS. This will help reinforce positive behaviors that have helped.

Specialized nursing care

- Participants in the intervention group will have access to a specialized nurse with many years of experience caring for rectal cancer patients. The nurse will speak with participants once before their surgery and walk them through the educational booklet.
- After surgery, the nurse will call participants 5 more times during the first 12 months – at 1 month, 3 months, 6 months, 9 months, and 12 months – to answer any questions, and review the diaries.
- Lastly, the nurse will have "office hours" once a week, where she will be available by telephone or by email to answer more urgent questions.
- It is important to remember that the role of this nurse is only to help with LARS care, and she does not replace a doctor for more urgent medical issues. The nurse will use her years of experience and professional judgment to decide what sort of issues might fall outside of her role.

Participants in both groups

- Participants in both the intervention and control groups will receive several questionnaires, which will allow us to understand if the supportive intervention is helping patients with their LARS.
- **Questionnaires** will be sent out once before surgery, and then 4 more times after surgery – **at 1 month, 3 months, 6 months, and 12 months.**
- Questionnaires can either be mailed to you, sent by email, or answered over the phone – whichever you prefer. If you choose to have the questionnaires mailed to you we will include an envelope and postage so that you can send back the completed questionnaires.
- You may receive telephone calls from our research coordinator to ensure that you have received the questionnaires.

Duration

All participants, whether part of the intervention group or control group, will be followed for the first 12 months after their surgery. The first questionnaire is to be completed just prior to surgery, and the final questionnaire 12 months after surgery. After the 12 months have passed, we will not contact you for any other reasons related to the study.

Reimbursements

Participants will receive $10 for each set of completed questionnaires, and $20 once all questionnaires are completed. The 10$ gift for each completed set of questionnaires will be sent to participants as soon as the completed questionnaire is received by the research team.

Risks, Discomforts and Side-Effects:

By taking part in this study, you should be at no increased risk for unwanted side-effects or discomfort. No new medication is being recommended for the purpose of the study. All of the treatment strategies recommended in the educational booklet and by the specialized nurse are considered "standard" treatments, and are usually already discussed by the treating surgeon. If any of the questions make you uncomfortable you may choose not to answer them, or, if you become upset you may contact the PI, the nurse or any member of the research team.

Benefits:

If you are part of the supportive intervention group, we hope (and anticipate) that your knowledge regarding LARS will increase, and that you might be more active in the care of your LARS. Because of this, you may experience improvements in your quality of life and even in the severity if your LARS symptoms. If you are part of the control group, you will be less likely to get any benefit, as you are acting as a comparison group to see if our intervention is making a difference. At the end of the study, regardless of the findings, we will make our educational booklet publicly available to all participants.
That being said, we cannot guarantee that you will receive any direct benefits from this study.

Voluntary participation/withdrawal:

Your participation in this research project is voluntary. Therefore, you may refuse to participate. You may also withdraw from the study at any time, without giving any reason.

Your decision not to participate in the study, or to withdraw from it, will have no impact on the quality of care and services to which you are otherwise entitled, or on your relationship with the doctor in charge of this research study or the clinical team.

If you withdraw or are withdrawn from the study, the information collected during the study will nonetheless be stored, analyzed or used to protect the scientific integrity of the research project.

Unexpected discoveries

Any new findings that could influence your decision to stay in the research project will be shared with you as soon as possible. If this happens, we will contact you to set up a visit with your treating surgeon or oncologist. This physician will share this information with you and plan your subsequent management.

Confidentiality:

While you take part in this research study, the researcher in charge and study staff will collect and store personal identifiable information about you in a file for the purpose of the research study. Only information necessary for the research study will be collected.

All the information collected about you during the study will remain confidential within the limits of the Law. To protect your identity, your name and identifying information will be replaced with a code number that has no identifying information. The code will be linked to your hospital ID and the link between the code and your identity will be held by the researcher in charge of the study. No information that discloses your identity will be allowed to leave the institution. Your study information will be kept in a de-identified manner for 10 years by the researcher in charge of the study, after which it will be anonymized. The data will be held in a password protected file and a password protected computer in locked offices at the Jewish General Hospital. After 10 years, the anonymized data will be kept indefinitely by the Investigator for the purposes of future research in colorectal surgery 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.

The study information may also be used for other reasons related to the study or to help in the development of future studies.

The study information could be printed/published in medical journals or shared with other people at scientific meetings, but your identity will not be revealed.

For monitoring, control and protection purposes, your research study file as well as your medical file could be checked by a person authorized by the Research Ethics Committee of the CIUSSS du Centre-Ouest-de-l'ile de Montreal or by persons mandated by authorized public agencies. These persons are bound by a confidentiality agreement.

For safety purposes, and in order to communicate information that is required in order to protect your well-being, the principal researcher of this study will keep separate from the research documents your personal information including your name, contact information, the date your participation in the study began and when it ended for the period of ten years after the end of the study. The data will be kept in a de-identified manner for 10 years following study completion and then it will be anonymized for use in future studies on colorectal surgery. 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.

You have the right to look at your study file in order to check the information gathered about you and to correct it, if necessary, as long as the study researcher or the institution keeps this

information. However, you may only have access to certain information once the study has ended so that the quality of the research study is protected.

Should you suffer any harm:

By agreeing to participate in this research study, you do not give up any of your legal rights nor discharging the doctor in charge of this research study or the institution of their civil and professional responsibilities.

Investigator Compensation

The researcher in charge of this study has been awarded funding from a various professional medical societies and research granting agencies, to help cover the cost of running the study. The funds have been deposited into a research and development account.

Contact information or questions:

If you have any questions regarding the study, you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of the following:

Dr. Marylise Boutros, Primary Investigator
Jewish General Hospital
3755 Cote Ste Catherine G-317
Montreal, QC, H3T 1E2
T: 514-340-8222 ext. 22773
mboutros@jgh.mcgill.ca

Dr. Richard Garfinkle, Co-Investigator
3755 Cote Ste Catherine G-317
Montreal, QC, H3T 1E2
T: 514-515-1995
richard.garfinkle@mail.mcgill.ca

Sarah Sabboobeh, Research Coordinator
3755 Cote Ste Catherine G308
Montreal, QC, H3T 1E2
T: 514-340-8222 ext 22773
Sarah.sabboobeh@ladydavis.ca

For all questions regarding your rights as a research participant for this study, or if you have comments or wish to make a complaint, you may contact the Local Commissioner of Complaints and Quality of Services of the CIUSSS du Centre-Ouest-de-l'ile-de-Montreal at 514-340-8222 ext. 24222.

STATEMENT OF CONSENT
Impact of a Patient-Centered Program for Low Anterior Resection Syndrome

I have reviewed the information and consent form. Both the research study and the information contained in the consent form were explained to me. All my questions were answered, and I was given sufficient time to make a decision. After reflection, I consent to participate in this research study in accordance with the conditions stated above.
I authorize the research study team to have access to my medical record and biopsy results for the purposes of this study. I do not give up any of my legal rights by signing this consent form.

I agree to be re-contacted by the study team in the future regarding further participation in this study or to be asked about participation in other studies. Agreeing to be re-contacted does not mean I have to participate in these other studies.

YES NO INITIALS ☐

Name of the Participant Signature

Date

Consent form administered and explained in person by:

Name of the person obtaining consent Signature

Date

I certify that this information and consent form were explained to the research participant, and that the questions the participant had were answered. I undertake, together with the research team, to respect what was agreed upon in the information and consent form, and to give a signed and dated copy of this form to the research participant.

Name of the Investigator
Signature Date

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **Yes – page 1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **Yes – page 3 and 14**
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support **Yes – page 21**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **Yes – page 21**
	5b	Name and contact information for the trial sponsor **Not applicable**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities **Not applicable**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **Yes – pages 5 and 6**

	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses **Yes – page 7**
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **Yes – pages 7, 8 and 9**

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **Yes – page 7**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **Yes – page 7**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **Yes – pages 8, 9 and 10**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **Not applicable**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **Yes – pages 10 and 13**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **Yes – pages 8 and 9**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **Yes – pages 10, 11 and 12**

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) **Yes – Figures 1 and 2**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **Yes – page 13**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **Yes – page 13**

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **Yes – page 7 and 8**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **Yes – page 7 and 8**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **Yes – page 7 and 8**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **Yes – page 10**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **Not applicable**

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **Yes – pages 10, 11 and 12**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **Yes – page 10**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **Yes – page 13**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **Yes – page 13**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **Yes – page 13**
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **Not performed**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **Not applicable**

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **Yes – page 16**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) **Yes – page 16**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **Not applicable**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **Yes – page 21**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators **Yes – page 17**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **Yes – pages 16 and 17**
	31b	Authorship eligibility guidelines and any intended use of professional writers **Not applicable**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **Yes – page 17**

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates **Not applicable**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **Not applicable**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.