PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Development and Evaluation of a Patient-Centered Program for Low Anterior Resection Syndrome: Protocol for a Randomized Controlled Trial
AUTHORS	Garfinkle, Richard; Loiselle, Carmen; Park, Jason; Fiore Jr, Julio; Bordeianou, Liliana; Liberman, A.; Morin, Nancy; Faria, Julio; Ghitulescu, Gabriela; Vasilevsky, Carol-Ann; Bhatnagar, Sahir; Boutros, Marylise

VERSION 1 – REVIEW

REVIEWER	Linda Oostendorp University College London, Marie Curie Palliative Care Research Department
REVIEW RETURNED	02-Dec-2019

GENERAL COMMENTS	Thank you for the opportunity to review this well written manuscript, describing the evaluation of a newly developed intervention to support patients with LARS. The design is generally sound. There are a few issues that need clarification, in particular the issue of how the authors will deal with patients that will not develop LARS following surgery. ABSTRACT • There is no explanation of Low Anterior Resection Syndrome (LARS) in the abstract • Focus groups: according to the Methods section only one focus group was held METHODS AND ANALYSIS Phase 1: Study protocol for Proposed RCT Objectives (page 7): • the outcome 'patient satisfaction with the LPCP' has not been included here Participants and Setting (page 7): • According to the instructions for reviewers of study protocols, the dates of the study should be included in the manuscript. • Language: the exclusion criteria include 'inability to read and comprehend English or French'. This is not mentioned elsewhere in the manuscript which left me wondering whether study documents will be available in both languages? Standard care group (page 9): • Will patients in this group be told that they were randomized to the standard care group and will therefore not receive the

	intervention, or is there any form of deception? Will patients in this group get access to the informational booklet at the end of the study? • Will the intervention group also receive a paper copy (and/or instructions for online access) for the CCAC module mentioned? Data collection (page 10): • Will assessors be truly blinded if one of the questionnaires in the intervention group contains questions about satisfaction with the LPCP? Also, if questionnaires are completed over the phone patients may mention the booklet to the assessor. Outcomes (page 11): • The outcome 'Symptom Changes' has not been mentioned before. Statistical Analysis (page 13): • It is not clear whether the secondary outcome measures will also be analysed using GEE models. Power Analysis and Sample Size Calculations (page 13): • How will the authors deal with those patients who will not develop LARS? As stated in the Introduction, LARS can affect 70-90% of patients. Therefore, in each arm including 64 patients, it is to be expected that 6 (10%) to 19 (30%) patients will not develop LARS. Will these patients still be asked to complete all questionnaires? Does the sample size take this into account? Any effect of the LPCP could be diluted by including patients who may not benefit from the intervention. Phase 2: Development of Informational Booklet Focus group with patients/caregivers (pages 14-15): • Can the authors add some more details about the methodology, including a copy/description of the semi-structured interview guide? Did participants receive a copy of the booklet to review before the focus group? Were participants asked about the layout and structure, and other means of improving the booklet, just like the HCPs? Did caregivers participate in the interviews – no results from caregivers were reported? TABLES/FIGURES • Figure 1 and 2: please add the timing of all activities (1 month, 3 months, etc..) Typographical/grammatical errors: • Page 7, line 3: 'LCPC' should be 'LPCP' • Page 14, line 12: 'co-lead' should be 'co-led' • Page 15, line 35: Gastrointestinal Oncology • Page 15, line 54, 'compliment' should be 'complement' • Page 18, reference 7: proepertaive: 'preoperative'?

REVIEWER	Rebecca Fish University of Manchester, United Kingdom
REVIEW RETURNED	03-Dec-2019

GENERAL COMMENTS	This is a well written protocol for a well designed study. The aims and objectives are clearly identified and address an issue of clinical relevance to a large population of patients. The selected

	methods and outcome measures are appropriate to answer the study question. Minor points of further clarification I think the readers would benefit from a brief explanation of the concept of patient activation and it's relevance in this context. The methods state that the goals of the information booklet are to inform individuals with rectal cancer about post-operative bowel dysfunction. Is there a separate booklet for patients included with benign disease since the inclusion criteria states benign and malignant neoplasms are eligible for inclusion? The primary objective seems clear and the selected primary outcome measure is appropriate. However some of the secondary outcome measures would benefit from further justification and explanation of the questions they are intended to answer and the clinical relevance of these. Specifically, more detail is needed on the investigator generated knowledge MCQ. What is the objective of including this and what will it include specifically?

VERSION 1 – AUTHOR RESPONSE

REVIEWER #1

Reviewer 1, Comment 1: Thank you for the opportunity to review this well written manuscript, describing the evaluation of a newly developed intervention to support patients with LARS. The design is generally sound. There are a few issues that need clarification, in particular the issue of how the authors will deal with patients that will not develop LARS following surgery.

Response to Reviewer 1, Comment 1: Thank you for your review of our manuscript.

Reviewer 1, Comment 2: Abstract: There is no explanation of Low Anterior Resection Syndrome (LARS) in the abstract

Response to Reviewer 1, Comment 2: We have changed the first sentence of the abstract, which now reads: "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."

Reviewer 1, Comment 3: Abstract: Focus groups: according to the Methods section only one focus group was held

Response to Reviewer 1, Comment 3: We have changed that sentence in the Methods, which now reads: "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."

Reviewer 1, Comment 4: Objectives (page 7): the outcome 'patient satisfaction with the LPCP' has not been included here

Response to Reviewer 1, Comment 4: We have added this to the sentence on objectives, which now reads: "Secondary objectives include the effects of a LPCP on patient activation, bowel function, emotional distress, patient knowledge, and satisfaction with LARS care."

Reviewer 1, Comment 5: Participants and Setting (page 7): According to the instructions for reviewers of study protocols, the dates of the study should be included in the manuscript.

Response to Reviewer 1, Comment 5: The following sentence was added to that paragraph: “The study is estimated to be open from November 2019 to November 2022.” This estimation is based on the sample size requirement, the anticipated number of participating institutions, and the 1-year follow-up needed for each patient.

Reviewer 1, Comment 6: Participants and Setting (page 7): Language: the exclusion criteria include ‘inability to read and comprehend English or French’. This is not mentioned elsewhere in the manuscript which left me wondering whether study documents will be available in both languages?

Response to Reviewer 1, Comment 6: Yes; all study documents (including the informational booklet) were developed in English and French, as the lead site is located in Montreal, Quebec, Canada – a hospital that serves both English and French speaking patients. We have made several additions throughout the manuscript to emphasize this point. In the Study Protocol on page 8, where the LARS Patient-Centered Program is described, we added a sentence at the end of the paragraph on Informational Booklet and Patient Diaries, as follows: “The booklet was then translated into French and underwent a similar evaluation process.” In the next paragraph on Nursing Support, we emphasized the fact that the support nurse is also bilingual, with the following addition: “The study nurse (bilingual in English and French) has expertise in rectal cancer management…”. We also made an addition to the Outcomes section on page 8, which now reads: “The PROM package for each time-point (available in both English and French) will either be mailed to participants, disseminated via email…”. Finally, in part 2 of the manuscript (detailing the Developing of the LARS Patient-Centered Program), we have added the following statement in the last paragraph: “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.”

Reviewer 1, Comment 7: Standard care group (page 9): Will patients in this group be told that they were randomized to the standard care group and will therefore not receive the intervention, or is there any form of deception? Will patients in this group get access to the informational booklet at the end of the study?

Response to Reviewer 1, Comment 7: Yes; patients randomized to the standard care group will know that they are not receiving the full intervention. We are giving them a copy of the “Living with Colorectal Cancer” module from the Colorectal Cancer Association of Canada, which may allow them to feel that they are receiving something “in addition” to usual care. However, because they will not have access to the LARS support nurse, we cannot fully deceive them into thinking that they are in the intervention arm. Patients will be informed that the booklet will be made available to them once the trial is complete. We have added the following to the paragraph on Standard Care Group, as follows: “Participants in the standard care group will be told that they can have access to the informational booklet when the study is complete. “

Reviewer 1, Comment 8: Standard care group (page 9): Will the intervention group also receive a paper copy (and/or instructions for online access) for the CCAC module mentioned?

Response to Reviewer 1, Comment 8: We ultimately decided that we would not give intervention group patients the CCAC module. There are already a lot of reading materials (between the informational booklet, the diaries, and the PROMs, which in and of themselves takes time to read and fill out at each time point); thus, we did not want to overload them with any more reading material that may dilute the impact of the interventional tool. In theory, the CCAC module is publicly available

online as well. The use of the CCAC module in the standard care group was more to make them feel that they are receiving something for the trial as well.

Reviewer 1, Comment 9: Data collection (page 10): Will assessors be truly blinded if one of the questionnaires in the intervention group contains questions about satisfaction with the LPCP? Also, if questionnaires are completed over the phone patients may mention the booklet to the assessor.

Response to Reviewer 1, Comment 9: Thank for you noticing this. There was a small error in the Satisfaction paragraph. The satisfaction questionnaire is measuring satisfaction with the LARS care received by the patient over the study period (i.e. how satisfied they were with the information they received on LARS, and with the support they received for LARS). It is therefore not specific to patients in the LARS Patient-Centered Program. We have re-phrased this paragraph, which now reads: "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." With regards to patients mentioning their group allocation over the phone to the data entry coordinators, we do not believe this will be a major issue. Patients will be instructed and reminded to keep their treatment allocation concealed.

Reviewer 1, Comment 10: Outcomes (page 11): The outcome 'Symptom Changes' has not been mentioned before.

Response to Reviewer 1, Comment 10: We have added Symptom Change as a secondary objective in the Objectives paragraph, as follows: "Secondary objectives include the effects of a LPCP on symptom change, patient activation, bowel function, emotional distress, patient knowledge, and satisfaction with LARS care."

Reviewer 1, Comment 11: Statistical Analysis (page 13): It is not clear whether the secondary outcome measures will also be analysed using GEE models.

Response to Reviewer 1, Comment 11: Thank you for raising this to our attention, as it was not clear in the manuscript. GEE models will be used to estimate the effect of the intervention on QoL and bowel function scores. Both of these outcomes are measured at multiple time-points postoperatively (1, 3, 6, and 12 months), and represent the two most significant outcomes for this study. For the remaining secondary outcomes, we will perform pairwise comparisons at different time-points, and will not use GEE models. The use of GEEs for correlated data becomes less vital as the number of observations decreases. Furthermore, GEEs help account for possible missing data throughout the longitudinal follow-up, as it can use the correlation structure to estimate an individual's response at a later time-point; this issue is most important for the primary outcome, as it is the only outcome for which the trial will be adequately powered to study. We have made the following revision in the Statistical Analysis section: "The treatment effect on global QoL and bowel function will be modeled using generalized estimating equations (GEE).22 This method accounts for… For the remaining secondary outcomes, pairwise comparisons will be performed at various time-points."

Reviewer 1, Comment 12: Power Analysis and Sample Size Calculations (page 13): How will the authors deal with those patients who will not develop LARS? As stated in the Introduction, LARS can affect 70-90% of patients. Therefore, in each arm including 64 patients, it is to be expected that 6 (10%) to 19 (30%) patients will not develop LARS. Will these patients still be asked to complete all questionnaires? Does the sample size take this into account? Any effect of the LPCP could be diluted by including patients who may not benefit from the intervention.

Response to Reviewer 1, Comment 12: While it is possible that not all patients in the study will meet the definition of LARS (based on the LARS score), it can be expected that close to all patients will

experience some degree of bowel dysfunction. To somewhat mitigate this issue, we have limited the study population to those who had a diverting loop ileostomy, and who are now undergoing loop ileostomy closure. Patients who were diverted are typically the highest risk for LARS (diversion is commonly used in patients who have low tumors / low anastomoses, and who received neoadjuvant radiation therapy – which are the two greatest risk factors for LARS). Thus, this should be a patient population most likely to develop LARS.

Reviewer 1, Comment 13: Focus group with patients/caregivers (pages 14-15): Can the authors add some more details about the methodology, including a copy/description of the semi-structured interview guide? Did participants receive a copy of the booklet to review before the focus group? Were participants asked about the layout and structure, and other means of improving the booklet, just like the HCPs? Did caregivers participate in the interviews – no results from caregivers were reported?

Response to Reviewer 1, Comment 13: The interview guide for both the focus group and the semi-structured interviews have been added as Supplementary Files at the end of the Manuscript file, and are referenced accordingly in the text of the manuscript.
Re: copy of the booklet before the focus group, yes – participants were given two copies (one for the patient, one for his/her caregiver) of the booklet three weeks prior to the focus group. Healthcare professionals were given a similar time-period to review the booklet. The following has been added to the Focus Group paragraph: “Each participant/caregiver was given two copies of the informational booklet and allowed three weeks to review the booklet and generate their own thoughts.” Later on in the Semi-Structured Interviews paragraph, we have added the following: “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.”
Re: structure and layout of the booklet, it was asked of patients in several different ways. In the interview guide for the focus group, some of the questions that pertained to structure and layout (directly or indirectly) included:
“Overall what is your impression of the booklet?”
“What did you like / not like about the booklet?”
“Was there any topic about LARS that was discussed in too much / too little detail?”
“How was the overall length of the booklet?”
This can now be found in the recently added interview guide, referenced in the text of the manuscript. During the discussion, the layout and structure were brought up and discussed as well.
Re: caregivers participation in the interviews, yes – they were actively involved in the focus group. The overall themes generated from the focus group reflect the thoughts of both the patients and their caregivers; we have treated them as one group. We have clarified this in the text of the Focus Group results, which now reads: “The principal findings from the thematic analysis of the focus group are displayed in Table 3. Patients and their caregivers described the…”. The title of Table 3 should also reflect the fact that both patients and caregivers actively participated in the focus group: “Table 3 – Principal findings from thematic analysis of focus group with patients and caregivers”.

Reviewer 1, Comment 14: TABLES/FIGURES: Figure 1 and 2: please add the timing of all activities (1 month, 3 months, etc..)

Response to Reviewer 1, Comment 14: Both Figures 1 and 2 have been revised and include the timing of each activity.

Reviewer 1, Comment 15: Typographical/grammatical errors: Page 7, line 3: ‘LCPC’ should be ‘LPCP’. Page 14, line 12: ‘co-lead’ should be ‘co-led’. Page 15, line 35: Gastrointestinal Oncology. Page 15, line 54, ‘compliment’ should be ‘complement’. Page 18, reference 7: proepertaive: ‘preoperative’?

Response to Reviewer 1, Comment 15: All of these typos have been corrected. Thank you.

REVIEWER #2:

Reviewer 2, Comment 1: This is a well written protocol for a well designed study. The aims and objectives are clearly identified and address an issue of clinical relevance to a large population of patients. The selected methods and outcome measures are appropriate to answer the study question.

Response to Reviewer 2, Comment 1: Thank you for your comments and revision of this manuscript.

Reviewer 2, Comment 2: I think the readers would benefit from a brief explanation of the concept of patient activation and it's relevance in this context.

Response to Reviewer 2, Comment 2: Patient activation measures the degree of knowledge, skills, and confidence for self-management of healthcare. It has not been very well studied in surgical patients. However, in patients with chronic medical conditions, patient activation correlates well with improved medication adherence and decreased emergency room utilization. We believe that patient activation is a relevant measure in patients with LARS, which may also be considered to be a chronic medical condition. Given that LARS treatment requires very individualized care and troubleshooting, patients need to take an active role in their care in order to achieve the best results. As a secondary outcome, we believe that our informational and supportive intervention will increase patient activation for LARS, which may ultimately improve bowel function. We have added the following in the Outcomes section, under 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."

Reviewer 2, Comment 3: The methods state that the goals of the information booklet are to inform individuals with rectal cancer about post-operative bowel dysfunction. Is there a separate booklet for patients included with benign disease since the inclusion criteria states benign and malignant neoplasms are eligible for inclusion?

Response to Reviewer 2, Comment 3: No; there is only one booklet. Patients with benign neoplastic disease still have pre-cancerous lesions (e.g., polyps with high-grade dysplasia), and the information in the booklet applies equally to them. With modern endoscopic and trans-anal techniques, it is rare to have to perform a restorative proctectomy for benign neoplastic disease, but we felt these patients (however few they may be) should be included. They are equally at risk for LARS as patients who undergo a restorative proctectomy for malignant neoplasm of the rectum. The surgery is identical, and the functional consequences are still present.

Reviewer 2, Comment 4: The primary objective seems clear and the selected primary outcome measure is appropriate. However some of the secondary outcome measures would benefit from further justification and explanation of the questions they are intended to answer and the clinical relevance of these. Specifically, more detail is needed on the investigator generated knowledge MCQ. What is the objective of including this and what will it include specifically?

Response to Reviewer 2, Comment 4: In the Outcomes section, we have added 2-3 sentences for some of the secondary outcomes to explain their relevance and context for the current study. The

outcomes “quality of life”, “symptom change”, “bowel function” and “satisfaction with LARS care” were not expanded upon, as we feel their inclusion in the current study requires no further explanation. However, we are happy to expand on them for the Reviewer should she feel this is necessary.
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.”
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.”
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.”

VERSION 2 – REVIEW

REVIEWER	Linda Oostendorp University College London, Marie Curie Palliative Care Research Department
REVIEW RETURNED	07-Jan-2020

GENERAL COMMENTS	Thank you for your detailed responses. I am happy with the revisions made and have no further comments.

REVIEWER	Rebecca Fish University of Manchester, UK
REVIEW RETURNED	06-Jan-2020

GENERAL COMMENTS	Thank you to the authors for thoroughly addressing the points raised in the first review. The revisions have added clarity to the manuscript which I am now recommending is accepted for publication. I look forward to seeing the results of this study.