PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Pathway Of Low Anterior Resection syndrome relief after Surgery (POLARiS) feasibility trial protocol: A multicentre, feasibility cohort study with embedded randomised control trial to compare sacral neuromodulation and transanal irrigation to optimised conservative management in the management of major Low Anterior Resection Syndrome following rectal cancer treatment.
AUTHORS	Coxon-Meggy, Alexandra; Vogel, Irene; White, Judith; Croft, Julie; Corrigan, Neil; Meggy, Alun; Stocken, Deborah; Keller, Deborah; Hompes, Roel; Knowles, Charles; Quyn, Aaron; Cornish, Julie

VERSION 1 – REVIEW

REVIEWER	Dulskas , Audrius National Cancer Institute
REVIEW RETURNED	09-Aug-2022

GENERAL COMMENTS	I would like to congratulate you with this great idea. I have only few minor issues: INTRODUCTION --well written - no comments. METHODS --How did you decide to do the 9 mo inclusion? Why is it not one year? 6 mo? --Why are you including the high anterior resection? Following Delphi consensus LARS is nicely described and low anterior resection is a must for diagnosis of LARS. --How are going to invite patients to enter the trial - the goal is to include 200 patient cohort and the prevalence of major LARS is high. --It would be interesting to include the Placebo arm - without any treatment or recommendations.

REVIEWER	Pape, Eva Ghent University
REVIEW RETURNED	17-Oct-2022

GENERAL COMMENTS	Thank you for this very interesting feasibility trial protocol about a pathway Of Low Anterior Resection syndrome relief after Surgery (POLARiS). I have some additional comments/questions regarding the protocol - There are some grammatical error regarding the citations in the text. - Abstract:

	o I would state that sphincter saving curative treatment can result in … instead of curative treatment - Methods and analysis o A repetition of the sentence …offering two or three-arm randomisation depending on eligibility. o In the introduction you are talking about rectal cancer yet you are also including sigmoid cancer patients. Maybe explain this in the introduction as well. o An exclusion criteria is: site unable to offer TAI/SNM as a treatment. Why do you include this sites in the study? o You define physiotherapy as a conservative treatment but several intervention pathways in literature do not catalogue physiotherapy as conservative treatment. So maybe explain why you do so. o Who will give the optimised conservative management? o TAI: will you use several devices or just one device? Is it possible that the frequency of TAI varies? o The assessment will be done at recruitment, 3, 6, 9 and 12 months. Are you already including patients in the intervention while doing the assessment? o How will you evaluate the interventions?

VERSION 1 – AUTHOR RESPONSE

Responses to reviewer Dr Audrius Dulskas:

-How did you decide to do the 9 mo inclusion? Why is it not one year? 6mo?

The 9-month inclusion was chosen to optimise recruitment without running into the planned main trial. This is the feasibility study for the now funded larger POLARiS trial which will be based on the same study design with some changes depending on the outcome of the feasibility trial. We wanted to ensure that we had enough data available during the set up of the main trial from the feasibility trial to ensure the study design was optimised. We have not put this in the protocol.

-Why are you including the high anterior resection? Following Delphi consensus LARS is nicely described and low anterior resection is a must for diagnosis of LARS.

Thank you for identifying this important area which needs clarifying. We have explained our rationale for including HAR in the introduction section. In brief, we decided to include patients who had undergone a HAR or sigmoid colectomy for several reasons:

1) The level of the bowel division for a planned high anterior resection (HAR) may vary and if a stapled anastomosis is being performed then there will have been some rectal dissection and potentially some impact on rectal function. We know from the literature that there are patients with a HAR who have LARS symptoms and this needs to be further characterised.
   We will be collecting data on the height of the tumour, name of the operation performed and the height of the anastomosis as part of the study.
2) We believe that there are multiple factors that contribute to LARS and it is currently not clear how much of a contribution the removal of the “recto-sigmoid break” may be as a risk factor for the development of major LARS. This will allow us to further investigate this.

-How are going to invite patients to enter the trial – the goal is to include 200 patient cohort and the prevalence of major LARS in high.

There is significant variation in the incidence within the literature of LARS. We have developed the concept of the cohort study to allow us to clarify this and to recruit patients with major LARS into the RCT. If the incidence of LARS is less than 40% we may have to screen additional patients and this will obviously impact in the design of the main study.

Eligibility into the RCT will be based on the LARS score (major LARS) which as stated is estimated to be as high as 40%. If we find 40% of patients have major LARS in this study we are not expecting all participants to go on to be randomised. There will be a number of patients who are not eligible as they may not have received any 'conservative treatment' as we know from previous work that the identification and treatment of LARS is very variable and, in some places, quite poor. We also expect that some participants will not wish to take part in the RCT either due to the acceptability of the treatment options (for example transanal irrigation studies have struggled to recruit in the UK as it is not considered an acceptable treatment by some patients) or as the participant does not feel that their LARS score correlates with their quality and experience of daily life and do not wish for any intervention or treatment.

-It would be interesting to include the Placebo arm – without any treatments or recommendations.

This is something we explored in focus groups when the trial was in its early design phases and the patient participants of these groups did not think it would be acceptable to offer no treatment. As such, the optimised conservative management arm was designed. The hope is this will improve recruitment to the RCT as all participants should receive a treatment which improves their LARS.

Responses to reviewer Eva Pape:

-There are some grammatical error regarding the citations in the text.

Thank you for bringing these to our attention. The text and citations have been reviewed and corrected.

-Abstract: I would state that sphincter saving curative treatment can result in… instead of curative treatment.

We agree with this comment and have amended the abstract accordingly. Thank you.

-A repetition of the sentence… offering two or three-arm randomisation depending on eligibility.

Thank you for bringing this to our attention. This method section has been updated to remove this repetition.

-In the introduction you are talking about rectal cancer yet you are also including sigmoid cancer patients. Maybe explain this in the introduction as well.

We have now clarified and explained the rationale for this in the introduction.

-An exclusion criteria is: site unable to offer TAI/SNM as a treatment. Why do you include this sites in the study?

For the feasibility study we have included 4 centres all of which are able to offer at least TAI and three centres also offer SNM. The pragmatic design of the trial aims to provide data and evidence which can be used across the UK, at present there are very few centres which offer SNM and not all hospitals are able to refer on to those centres which do perform it. As such we felt that including sites who may not be able to offer SNM would enable us to produce evidence and later guidance which is

available to all patients. Sites which are unable to perform at least one option of SNM or TAI are not eligible for the feasibility study or the main trial.

-You define physiotherapy as a conservative treatment but several intervention pathways in literature do not catalogue physiotherapy as conservative treatment. So maybe explain why you do so.

A sentence on the provision of physiotherapy has been added to the 'Interventions' 'Optimised Conservative Management' section. The NICE research call and HTA funding theme specifically included physiotherapy in conservative care for LARS. As such there was not the option to have physiotherapy as a separate intervention as it is not a core outcome of the trial. We have included it as part of the OCM as there is evidence that it can be beneficial in LARS patients but as it isn't a key trial intervention we cannot dictate that the site must offer it.

-Who will give the optimised conservative management?

We have now added a statement on this to the 'Interventions' 'Optimised Conservative Management' section. OCM will be delivered by a suitably qualified healthcare professional with experience of caring for patients with bowel dysfunction and following the POLARiS OCM training. This could include a specialist nurse, physiotherapist, surgeon or gastroenterologist depending on the local set up.

-TAI: will you use several devices or just one device? Is it possible that the frequency of TAI varies?

We have clarified this is the 'Interventions' 'Transanal Irrigation' section. Any licenced TAI device is accepted within the trial as we know from previous studies that specifying a device can impact on recruitment. We will record the name of the device, volume of irrigation, prescribed frequency of treatment on the case report form. We will also be able to see through prescription records whether the participant is compliant with the prescribed course.

-The assessment will be done at recruitment, 3, 6, 9 and 12 months. Are you already including patients in the intervention while doing the assessment?

We believe this has been addressed in the study flow diagram and the 'Assessments' section. We have added a few words to further clarify. Please let us know if this is still unclear.

For participants who are in the cohort they will be sent the questionnaires at recruitment, 3, 6, 9 and 12 months, there will not be any clinical assessment. For those participants who are recruited from the cohort to the RCT they will be receive the same questionnaires at 3, 6, 9 and 12 months in addition to clinical assessments as outlined in the study flow diagram.

-How will you evaluate the interventions?

This has been clarified in the 'Assessments' section.

The interventions in the RCT will be evaluated using the LARS score, EQ-5D, EORTC QLQ-CR29 and QLQ-C20 and the MYMOP II. These was also be collected for all patients in the cohort on a 3-monthly basis.

VERSION 2 – REVIEW

REVIEWER	Dulskas , Audrius National Cancer Institute

REVIEW RETURNED	30-Nov-2022

GENERAL COMMENTS	The manuscript improved a lot. I have no further comments. Good luck with the study!

REVIEWER	Pape, Eva Ghent University
REVIEW RETURNED	15-Dec-2022

GENERAL COMMENTS	I agree with the changes that have been made.