

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-064248
Article Type:	Protocol
Date Submitted by the Author:	28-Jun-2022
Complete List of Authors:	Vogel, Irene; Amsterdam University Medical Centres Coxon-Meggy, Alexandra; Cardiff and Vale University Health Board, Colorectal Surgery; Cardiff University School of Medicine White, Judith; Cardiff University School of Medicine, Cedar Croft, Julie; University of Leeds, Clinical Trials Research Unit, Leeds Institute of Clinical Trials Corrigan , Neil; University of Leeds Clinical Trials Research Unit Meggy, Alun; Cardiff and Vale University Health Board Stocken, Deborah; University of Leeds Clinical Trials Research Unit Quyn, Aaron; Leeds Teaching Hospitals NHS Trust; University of Leeds School of Medicine Knowles, Charles; Barts and the London SMD, Centre for Academic Surgery Cornish, Julie; Cardiff and Vale University Health Board, Colorectal Surgery
Keywords:	Colorectal surgery < SURGERY, Clinical trials < THERAPEUTICS, Gastrointestinal tumours < GASTROENTEROLOGY

SCHOLARONE™
Manuscripts

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

Irene Vogel ¹, Alexandra Harriet Coxon-Meggy ^{2,3}, Judith White², Julie Croft⁴, Neil Corrigan⁴, Alun Meggy³, Deborah Stocken⁴, Aaron Quyn^{5,6}, Charles Knowles⁷, Julie Cornish² *on behalf of the POLARiS Trial Development Group*⁸

Corresponding author: Alexandra Coxon-Meggy
Duthie Ward,
University Hospital of Wales
Heath Park
Cardiff
CF14 4XW
Telephone: 07534518625
Email: Alexandra.coxon2@wales.nhs.uk

Key Words: rectal cancer, Low Anterior Resection Syndrome, protocol, sacral neuromodulation, transanal irrigation

Word Count: 3214

¹ Amsterdam University Medical Centres, Duivendrecht, Noord-Holland, NL

² Cardiff University School of Medicine, Cardiff, UK

³ Cardiff & Vale University Health Board, Cardiff, UK

⁴ University of Leeds, Clinical Trials Research Unit, Leeds Institute of Clinical Trials, Leeds, UK

⁵ University of Leeds School of Medicine, Leeds, West Yorkshire, UK

⁶ Leeds Teaching Hospitals NHS Trust, Leeds, West Yorkshire, UK

⁷ Barts and the London SMD, Centre for Academic Surgery, Royal London Hospital, Whitechapel, London, UK

⁸ Trial Development Group: Vogel I, Coxon-Meggy AH, White J, Croft J, Corrigan N, Meggy A, Hompes R, Keller D, Dale M, Withers K, Jayne D, Warwick A, Ng K-S, Hepburn J, Powell R, Torkington J, Stocken D, Quyn A, Knowles C, Cornish JA

ABSTRACT

Introduction

Rectal cancer is common with a 60% 5-year survival rate. Treatment usually involves surgery with or without neoadjuvant chemoradiotherapy or adjuvant chemotherapy. Curative treatment can result in debilitating changes to bowel function known as Low Anterior Resection Syndrome (LARS). There are currently no clear guidelines on the management of LARS with only limited evidence for different treatment modalities.

Methods & Analysis

Patients who have undergone an anterior resection for rectal cancer in the last 10 years will be approached for the study. The feasibility trial will take place in 4 centres with a 9-month recruitment window and 12 months follow up period. The primary objective is to assess the feasibility of recruitment to the POLARiS trial which will be achieved through assessment of recruitment, retainment and follow up rates as well as the prevalence of major LARS.

Feasibility outcomes will be analysed descriptively through the estimation of proportions with confidence intervals. Longitudinal patient reported outcome measures (PROMS) will be analysed according to scoring manuals and presented descriptively with reporting graphically over time.

Ethics & Dissemination

Ethical approval has been granted. The feasibility study is in the process of set up. The results of the feasibility trial will feed into the design of an expanded, international trial.

Trial registration number

CT05319054

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This feasibility trial is the first step in addressing a NICE research recommendation to assess the effectiveness of transanal irrigation and sacral neuromodulation in the treatment of major LARS
- The trial is pragmatically designed to optimise and assess recruitment and retainment
- This trial aims to add knowledge on the natural progression of low anterior resection syndrome over time
- This is a feasibility trial and will not be powered to answer whether TAI or SNM is more effective in the treatment of major LARS
- Not all patients with debilitating bowel dysfunction may be identified in the study due to the lack of QoL measures in the current LARS score

INTRODUCTION

Over 10,000 people are diagnosed with rectal cancer each year in the UK (1) with a five-year survival of just over 60%, which has risen by over 35% since the 1970s(2). Whilst the survival rate has vastly improved due to oncological and surgical advances, the adverse consequences of these treatments are now increasingly recognised. One such consequence is Low Anterior Resection Syndrome (LARS) which describes a constellation of bowel dysfunction symptoms including urgency, frequency, faecal incontinence, stool clustering and incomplete evacuation which have a significant impact on quality of life. It is estimated that around 75% of patients who have undergone an anterior resection, the commonest operation for rectal cancer, will be affected by LARS in the first year following surgery(3). Of those patients 25% will have persisting symptoms beyond 1 year, with half having symptoms up to 10 years(4). The severity of LARS is currently calculated using the validated LARS Score which defines LARS as 'no LARS' (score 0-20), minor LARS (score 21-29) and major LARS (score over 30) (5).

LARS was defined in 2012 (6) and whilst it is a widely accepted condition within coloproctology there is limited guidance on management. Patients are often not informed about the likelihood of changes to their bowel function following surgery and the chronicity of these changes (7). Due to the sensitive nature of LARS symptoms there is often a reluctance from patients to discuss their symptoms causing a barrier to treatment and may lead on to a downward spiral with isolation, anxiety and loss of relationships and intimacy(8).

The current treatment for LARS is largely based on that of faecal incontinence (FI), though it is worth noting that FI is only one potential component of LARS. Conservative management treatments including changes to diet, medications such as loperamide and enemas and physiotherapy techniques are the main stay of management. If these do not adequately improve the symptoms of LARS then transanal irrigation (TAI) or sacral neuromodulation (SNM) can be trialled. A recent systematic review looking at the impact of TAI on a range of bowel conditions including LARS suggested improved bowel function and a likely improvement in quality of life (QoL) but a lack of high quality evidence limited the review (9). Currently SNM is only licenced for use in FI, but there is evidence that significant improvements in function might be achieved in patients with LARS as well(10). A systematic review of 21 studies assessing the treatment options for LARS concluded that the existing quality of research was poor with only small studies on single treatments(11). The recent MANUEL project is the first study to address the variability in the treatment of LARS by setting out a clear management pathway (12). The lack of evidence regarding SNM and TAI remains an issue and has led to the National Institute for Clinical Excellence (NICE) identifying this as a research priority the treatment options for LARS (13). The recommendation was to assess effectiveness and safety of SNM and TAI compared to symptomatic treatment for people with major LARS following treatment for colorectal cancer.

The prevalence and natural history of LARS and its treatment strategies remain poorly understood. Clinician and patient awareness and compliance with available treatments remains unknown. The POLARiS trial is designed to investigate these specific interventions. Developed in parallel, this feasibility trial will describe the prevalence of LARS and test the POLARiS trial design to explore the feasibility of running a definitive, expanded randomised control trial.

OBJECTIVES

The objectives of the feasibility trial are to establish the prevalence of major LARS in patients up to 10 years following treatment for rectal cancer and to explore the study design of the trial prior to commencing an expanded, definitive trial. 3

METHODS AND ANALYSIS

Study Design

This feasibility trial is a multicentre cohort study with embedded randomised controlled trial (RCT) utilising the Trials within in a Cohort (TWiC) study design (14). The RCT is an open-label, parallel group trial offering two or three-arm randomisation depending on eligibility. This feasibility trial is a multicentre cohort study with embedded open-label, parallel group, randomised control trial, offering two- or three-arm randomisation options depending on eligibility criteria. Participating centres include Cardiff & Vale University Health Board, Leeds Teaching Hospitals NHS Trust, University Hospital Southampton NHS Trust and Aneurin Bevan Health Board. Cardiff & Vale Health Board will act as the trial sponsor. The trial protocol has been developed in line with the 2013 SPIRIT statement(15). The study design is demonstrated in figure 1. The trial will primarily establish the prevalence of LARS in the study sites, and then explore the feasibility to recruit, retain and follow-up patients. All study participants will initially be recruited to the cohort during the 9-month recruitment window. All cohort patients will be asked to complete a LARS score and quality of life questionnaires on recruitment and every 3 months for 12 months. If a participant within the cohort is identified as having major LARS according to their LARS score (score of 30 or more) they will be invited to the RCT. The trial treatments are optimised conservative management (OCM), transanal irrigation (TAI) and sacral neuromodulation (SNM).

Study Population

All patients who have had an anterior resection or in the last 10 years will be screened and a random selection of 50 eligible patients per participating site will be approached for this feasibility trial.

Eligibility criteria

Inclusion criteria for the cohort:

- Diagnosis of rectal or sigmoid cancer
- Low or high anterior resection (colorectal resection with anastomosis to the rectum)
- Functioning anastomosis
- 18+ years of age
- Primary surgery/reversal of ileostomy less than 10 years before recruitment
- Reversal of ileostomy at least 12 weeks prior to recruitment with at least a further 12 weeks of standard care to manage symptoms following reversal.
- Willing and able to provide valid informed consent

Exclusion criteria for the cohort:

- Inability to understand and complete study questionnaires independently
 - Due to cognitive or intellectual impairment
 - Due to insufficient English language skills

Patients eligible to join the cohort according to the above criteria will then be screened for eligibility to be randomised.

Inclusion criteria for the randomised controlled trial (all randomisation options):

- Recruited to cohort study

- Willing and able to provide valid informed consent for randomisation
- Major LARS
 - Defined as a LARS score of 30 or more
- Previous unsuccessful conservative treatment as determined by treating clinician and patient

Exclusion criteria for the randomised controlled trial (all randomisation options):

- Pregnancy
- No previous conservative treatment plan for the management of LARS
- Does not meet any treatment-specific criteria

Exclusion criteria for randomised controlled trial TAI-inclusive randomisation options (randomisation options 1 and 3):-

- Unable to perform TAI
- History of anastomotic leak with evidence of ongoing leak/sinus on postoperative gastrograffin enema
- Previous use of TAI for LARS
- Site unable to offer TAI as a treatment
- Any other contraindications advised by the care team, product manufacturer or distributor

Exclusion criteria for SNM-inclusive randomisation options (randomisation options 1 and 2)

- <12 months since primary cancer surgery
- Palliative disease
- Site unable to offer SNM as a treatment
- Previous SNM
- Specific contraindications to implantation
- Any other contraindications advised by the care team, product manufacturer or distributor

Randomisation

Cohort participants with a LARS score over 30 will be invited to take part in the RCT. Dependent on their eligibility to receive TAI or SNM, patients will be randomised in one of three randomisation options, all with equal allocation ratio. The trial will utilise multiple randomisation options such that ineligibility to one treatment does not exclude a patient from the whole trial.

Randomisation option 1: OCM vs SNM vs TAI

Randomisation option 2: OCM vs SNM

Randomisation option 3: OCM vs TAI.

Randomisation will be carried out by the person consenting the patient to the RCT. Blocked randomisation using variable block sizes will be performed to produce random treatment allocations. An automated 24-hour, online randomisation system will be developed and maintained by the Clinical Trials Research Unit at the University of Leeds. Due to the nature of the interventions, this is a non-blinded trial.

Interventions

Optimised conservative management

The Optimised Conservative Management (OCM) treatment programme has been designed for this feasibility trial using current evidence on the conservative treatment of LARS. The programme will include lifestyle advice, dietary changes, medication and physiotherapy. All research sites will undergo training on the POLARiS OCM treatment programme and will be supplied with the guides and patient booklets to use with their patients. Each treatment or management option delivered will be clearly recorded for every participant.

Transanal Irrigation

Transanal irrigation (TAI) will be commenced by an appropriately trained clinical nurse specialist. The choice and frequency of TAI will be guided by clinical expertise and evidence-based guidance(16) and will be recorded for every participant. Participants will undergo a period of training with their TAI device, during which time the device and volume can be changed to achieve optimal outcome for the patient.

Sacral Neuromodulation

Participants randomised to SNM will undergo temporary testing according to local protocol (either with temporary testing wire or with the tined lead(17). This testing phase typically lasts one to three weeks and seeks to evaluate acceptability and response (using symptoms diaries) prior to a permanent device being fitted. The temporary and permanent devices will be implanted by a qualified surgeon in sites that can offer SNM.

Assessments

The assessments are carried out at recruitment, and then at 3, 6, 9 and 12 months. The assessments being used are outlined in table 1 and are to be completed by the participant.

Table 1 Assessment tools

Assessment/Questionnaire	Description
LARS Score	Internationally validated five question assessment exploring different bowel dysfunction symptoms and their frequency. The overall score (maximum 42) corresponds to either no LARS (0-20), minor LARS (21-29) or major LARS (over 30). (18)
EQ-5D-5L	Designed and validated by Euroqol as a health-related quality of life tool that generates a single index value for health status. This score is also valuable in the assessment of health care evaluation and economic analysis.(19)
European Organisation for Research and Treatment of Cancer (EORTC) QLQ-CR29 QLQ-C20	Internationally validated cancer specific questionnaires. The EORTC produce cancer specific quality of life questionnaires (QLQ) which focus on the effects of diagnosis and treatments. The QLQ-C30(20) focusses on cancer whilst the CR29(21) is specific to colorectal cancer.
Measure Yourself Medical Outcomes Profile (MYMOP II)	Patient specific outcome tool in which the patient identifies two symptoms with the most significant impact on their quality of life. This tool allows for an individualised approach and measure regarding the identified symptoms to assess morbidity/adverse events related to treatment and occupational outcomes.(22)

Sample Size Estimation

Sample size requirement has been determined in terms of number of patients to be recruited to the cohort and number of site-months of recruitment.

A minimum of 200 patients is the target recruitment set across all investigational research sites in this cohort study. This sample size ensures a maximum 95% confidence interval half-width of 0.058 when estimating proportions in this cohort population, such as the prevalence of major LARS and the proportions of cohort patients who are eligible for, and recruited to, the RCT. This is sufficiently precise to inform sample size assumptions and expectations in the definitive POLARIS trial.

The aim is to observe a minimum of 36 site-months (4 sites recruiting for 9 months) of recruitment. This will provide sufficient precision of the Poisson parameter estimate of recruitment rate per site per month. With 200 patients recruited to the cohort over 36 site-months, the Poisson parameter estimate would be 5.55 patients recruited per site per month, with a 95% confidence interval half-width of 1.57 i.e. 95% CI:= (4.0, 7.1). This is sufficiently precise to inform recruitment rate assumptions and expectations in the POLARIS trial.

We have set a maximum of 60 patients to be recruited to the RCT to allow assessment of acceptability and crossover.

Outcome Measures

The objectives of the trial and the outcome measures those objectives will be assessed against are listed in table 2.

Table 2 Objects and outcome measures

Objectives	Outcome Measures	Endpoints
<p>Primary Objective To assess the feasibility of conducting the 'POLARIS' trial</p>	<ol style="list-style-type: none"> 1) Identify the recruitment rate to the cohort. 2) Assess the characteristics of patients recruited to the cohort. 3) Identify the prevalence of major LARS and onset from time of resection and time of radiotherapy. 4) Identify the eligibility and conversion to recruitment in the RCT including proportions recruited to the three randomisation options. 5) Describe the standard of care and variation across sites. 6) Retention/adherence rate: compliance of patient to the treatment program exploring potential crossover. 7) Follow up rate: willingness to complete and return outcome questionnaires and format of completion. 	<ol style="list-style-type: none"> 1) Baseline, 3 months, 6 months, 9 months 2) Baseline, 3 months, 6 months, 9 months 3) 9 months 4) Baseline, 3 months, 6 months, 9 months 5) 12 months 6) 3 months, 6 months, 9 months, 12 months 7) Baseline, 3 months, 6 months, 9 months, 12 months
<p>Secondary Objectives Clinical and patient reported outcomes</p>	<ol style="list-style-type: none"> 1) Patient reported LARS score, new LARS score variables, EORTC CR29 & QLQ 30, 	<ol style="list-style-type: none"> 1) Baseline, 3 months, 6 months, 9 months, 12 months

	EQ5D and MYMOP II at recruitment and every 3 months	
	2) Patient reported adverse events	2) Throughout study to 12 months
	3) Treatments offered, length of treatment, reasons for stopping	3) 3 months, 6 months, 9 months, 12 months

A screening log will be kept of all the patients who are invited to take part in the trial. Patients who do not wish to participate in the study will be asked if they would like to provide additional information on why they have declined.

The secondary objective of the trial is to characterise and define the LARS patient population. This will be achieved through longitudinal patient reported outcomes (see Data Collection), specifically calculating the variability (standard deviation) in these measures, in addition to collecting data on the current standard of care offered to patients with bowel dysfunction after anterior resection.

Adverse events relating to the interventions will be collected and reported in line with Good Clinical Practice. Usability data will be collected for TAI and SNM and analysed along with compliance to treatment and reasons for stopping if applicable.

Data Analysis

Feasibility outcomes will be analysed descriptively through the estimation of proportions with confidence intervals (CI). Patient characteristics will be reported descriptively as either proportions (CI) or mean (standard deviation, CI) /median (interquartile range).

Longitudinal PROMs will be scored according to scoring manuals and analysed descriptively and reported graphically over time. Standardised area under the curve will be calculated and reported. Hierarchical repeated measures modelling will include covariate adjustment for stratification factors.

Randomised treatment groups will be combined across the three randomisation options to describe variability in PROMs for SNM, TAI, OCM.

As a feasibility trial there will be no statistical testing carried out to compare randomised treatment groups. Rather the variability in measures will inform the statistical design of the definitive trial.

DATA COLLECTION AND MANAGEMENT

Data Collection

Data collection will be undertaken by an appropriately trained clinical researcher as outlined in the delegation log. Data including basic demographics, medical history and details of their cancer diagnosis and treatment will be collected through health records for all patients recruited to the cohort. A short interview will also be conducted to gather information regarding current and previous treatments they have received for LARS. Participants will be asked to complete the following assessments and questionnaires at recruitment and then every 3 months for 12 months. Assessments can be completed electronically or on paper dependent on patient choice.

Management and safety

The trial will be managed in accordance with the principles of Good Clinical Practice and the UK Policy Framework for Health and Social Care Research. An internal trial management group (TMG) will meet monthly over the duration of the study and its role is to develop the study documentation, determine the study activities and undertake the study activities. The wider TMG will meet every 2-3 months to support the data interpretation and dissemination. The TMG will ensure the study is running to time and that recruitment is on target.

Adverse events (AEs) relating to trial specific interventions will be recorded for the purpose of the study as well as reported to the study Sponsor (Cardiff & Vale University Health Board) and discussed by the TMG, any AEs related to devices will be reported to the Medicines and Healthcare products Regulatory Agency (MHRA) and product manufacturer. The process for reporting AEs is clearly outlined in the study protocol and will be verbally addressed at site initiation visits.

PATIENT AND PUBLIC INVOLVEMENT

Two lay representatives were involved in the protocol design and will sit on the Trial Management Group throughout the lifecycle of the trial. The trial protocol and patient related trial documents including the information sheets, consent forms, case report forms and OCM treatment pathway have all been reviewed by the trial's lay representatives.

ETHICS AND DISSEMINATION

The trial will be conducted in accordance to the principles of Good Clinical Practice and the Declaration of Helsinki (2013). This study was reviewed and approved by Wales REC1 (ref: 22/WA/0025).

Informed consent will be obtained from willing participants prior to entering the cohort and undertaking any study-specific procedures. Those participants who are eligible to enter the RCT will be invited to sign a second consent form prior to being randomised. Separate participant information sheets will accompany these two consent events. Intimate examinations of the rectum and anus may be required as part of the assessment for treatment for those participants in the RCT; participants will need to consent to this as per any intimate examination undertaken clinically. In addition to study specific consent, participants who are treated with TAI or SNM will be asked to give procedure specific consent for TAI and SNM.

Participant confidentiality will be ensured throughout the trial with all participant data being stored on password protected databases at Cardiff & Vale Health Board as the Sponsor site, and hard copies stored in accordance with GCP. Once recruited, participants will be assigned a study identifier which will be used in place of patient identifiable information in the study database. Patient identifiable information with participant ID numbers will be stored on a password protected database.

The outcomes of this feasibility trial will be analysed and adjustments made where necessary to the study design ahead of an expanded, definitive trial. The trial outcomes will also be disseminated to participants upon request and published on completion of the trial in a peer reviewed journal.

Collaborators

POLARIS feasibility Trial Management Group: Julie Cornish, Aaron Quyn, David Jayne, Charles Knowles, Jared Torkington, Deborah Stocken, Julie Croft, Judith White, Neil Corrigan, Alun Meggy, Alexandra Coxon-Meggy, Irene Vogel, Roel Hompes, Deborah Keller, Andrea Warwick, Kheng-Seong Ng, Julie Hepburn (PPI) & Ralph Powell (PPI).

Contributors

JC conceived, designed and drafted the original protocol. IV & JW helped design and draft the original protocol. AHC helped revise the protocol and contributed to the production of the final protocol for the feasibility trial. All authors agree to be accountable for all aspects of the work. All authors read and approved the final manuscript.

Funding

This study was funded by Bowel Research UK (charity number 1186061 grant number []

Competing interests

Non declared

Patient consent

Not required.

Ethics approval

Ethical approval for this study has been granted by the Wales Research Ethics Committee.

REFERENCES

1. Cancer Research UK. No Title [Internet]. Bowel Cancer Incidence Statistics. 2017. Available from: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/incidence#heading-Zero>
2. Cancer Research UK. No Title [Internet]. Bowel Cancer Survival Statistics. 2017. Available from: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/survival#heading-Zero>
3. Martellucci J, Sturiale A, Bergamini C, Boni L, Cianchi F, Coratti A, et al. Role of transanal irrigation in the treatment of anterior resection syndrome. *Tech Coloproctol* [Internet]. 2018;22(7):519–27. Available from: <https://doi.org/10.1007/s10151-018-1829-7>
4. Battersby NJ, Bouliotis G, Emmertsen KJ, Juul T, Glynne-Jones R, Branagan G, et al. Development and external validation of a nomogram and online tool to predict bowel dysfunction following restorative rectal cancer resection: the POLARS score. *Gut*. 2018 Apr;67(4):688–96.
5. Emmertsen KJ, Laurberg S. Low Anterior Resection Syndrome Score: Development and Validation of a Symptom-Based Scoring System for Bowel Dysfunction After Low Anterior Resection for Rectal Cancer. *Ann Surg* [Internet]. 2012;255(5). Available from: https://journals.lww.com/annalsofsurgery/Fulltext/2012/05000/Low_Anterior_Resection_Syndrome_Score_Development.17.aspx
6. Bryant CLC, Lunniss PJ, Knowles CH, Thaha MA, Chan CLH. Anterior resection syndrome. *Lancet Oncol*. 2012 Sep;13(9):e403-8.
7. Ridolfi TJ, Berger N, Ludwig KA. Low Anterior Resection Syndrome: Current Management and Future Directions. *Clin Colon Rectal Surg* [Internet]. 2016 Sep;29(3):239–45. Available from: <https://pubmed.ncbi.nlm.nih.gov/27582649>

- 1
 - 2
 - 3
 - 4
 - 5
 - 6
 - 7
 - 8
 - 9
 - 10
 - 11
 - 12
 - 13
 - 14
 - 15
 - 16
 - 17
 - 18
 - 19
 - 20
 - 21
 - 22
 - 23
 - 24
 - 25
 - 26
 - 27
 - 28
 - 29
 - 30
 - 31
 - 32
 - 33
 - 34
 - 35
 - 36
 - 37
 - 38
 - 39
 - 40
 - 41
 - 42
 - 43
 - 44
 - 45
 - 46
 - 47
 - 48
 - 49
 - 50
 - 51
 - 52
 - 53
 - 54
 - 55
 - 56
 - 57
 - 58
 - 59
 - 60
8. Kupsch J, Kuhn M, Matzel KE, Zimmer J, Radulova-Mauersberger O, Sims A, et al. To what extent is the low anterior resection syndrome (LARS) associated with quality of life as measured using the EORTC C30 and CR38 quality of life questionnaires? *Int J Colorectal Dis* [Internet]. 2019;34(4):747–62. Available from: <https://doi.org/10.1007/s00384-019-03249-7>
9. Mekhael M, Kristensen HØ, Larsen HM, Juul T, Emmanuel A, Krogh K, et al. Transanal Irrigation for Neurogenic Bowel Disease, Low Anterior Resection Syndrome, Faecal Incontinence and Chronic Constipation: A Systematic Review. *J Clin Med*. 2021 Feb;10(4).
10. Huang Y, Koh CE. Sacral nerve stimulation for bowel dysfunction following low anterior resection: a systematic review and meta-analysis. *Color Dis* [Internet]. 2019 Nov 1;21(11):1240–8. Available from: <https://doi.org/10.1111/codi.14690>
11. Dulskas A, Smolskas E, Kildusiene I, Samalavicius NE. Treatment possibilities for low anterior resection syndrome: a review of the literature. *Int J Colorectal Dis* [Internet]. 2018;33(3):251–60. Available from: <https://doi.org/10.1007/s00384-017-2954-x>
12. Christensen P, Im Baeten C, Espín-Basany E, Martellucci J, Nugent KP, Zerbib F, et al. Management guidelines for low anterior resection syndrome - the MANUEL project. *Colorectal Dis* [Internet]. 2021/01/24. 2021 Feb;23(2):461–75. Available from: <https://pubmed.ncbi.nlm.nih.gov/33411977>
13. National Institute for Health and Care Excellence [NICE]. Colorectal Cancer [Internet]. 2020. Available from: <https://www.nice.org.uk/guidance/ng151/resources/colorectal-cancer-pdf-66141835244485>
14. Relton C, Torgerson D, O’Cathain A, Nicholl J. Rethinking pragmatic randomised controlled trials: introducing the cohort multiple randomised controlled trial design. *BMJ* [Internet]. 2010;340. Available from: <https://www.bmj.com/content/340/bmj.c1066>
15. Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* [Internet]. 2013;346. Available from: <https://www.bmj.com/content/346/bmj.e7586>
16. Emmanuel A, Collins B, Henderson M, Lewis L, Stackhouse K. Decision Guide for the use of rectal/transanal irrigation in adults [Internet]. MacGregor Healthcare; 2020. Available from: https://www.macgregorhealthcare.com/wp-content/uploads/2021/05/Decision-Guide_2020_UK_new.pdf
17. Matzel KE, Chartier-Kastler E, Knowles CH, Lehur PA, Muñoz-Duyos A, Ratto C, et al. Sacral Neuromodulation: Standardized Electrode Placement Technique. *Neuromodulation*. 2017 Dec;20(8):816–24.
18. Juul T, Battersby NJ, Christensen P, Janjua AZ, Branagan G, Laurberg S, et al. Validation of the English translation of the low anterior resection syndrome score. *Color Dis Off J Assoc Coloproctology Gt Britain Irel*. 2015 Oct;17(10):908–16.
19. NICE. Guide to the methods of technology appraisal 2013 [Internet]. 2013. Available from: <https://www.nice.org.uk/process/pmg9/chapter/foreword>
20. Groenvold M, Klee MC, Sprangers MA, Aaronson NK. Validation of the EORTC QLQ-C30 quality of life questionnaire through combined qualitative and quantitative assessment of patient-observer agreement. *J Clin Epidemiol*. 1997 Apr;50(4):441–50.
21. Whistance R, Conroy T, Chie W-C, Costantini A, Sezer O, Koller M, et al. Clinical and psychometric validation of the EORTC QLQ-CR29 questionnaire module to assess health-

- 1
2
3 related quality of life in patients with colorectal cancer. *Eur J Cancer*. 2009 Sep 1;45:3017–26.
4
5 22. Measures M. Measure Yourself Medical Outcomes Profile [Internet]. 2021. Available from:
6 <https://www.meaningfulmeasures.co.uk/mymop>
7
8 23. Walters SJ, dos Anjos Henriques-Cadby I, Bortolami O, Flight L, Hind D, Jacques RM, et al.
9 Recruitment and retention of participants in randomised controlled trials: a review of trials
10 funded and published by the United Kingdom Health Technology Assessment Programme. *BMJ*
11 *Open* [Internet]. 2017;7(3). Available from: <https://bmjopen.bmj.com/content/7/3/e015276>
12
13
14
15

16 **FIGURE LEGEND**

17 Figure 1 - Flow diagram to outline the study design for POLARiS Feasibility
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Setting: 4 sites (England & Wales) **Inclusion criteria:** Diagnosed with rectal or sigmoid cancer, left-sided resection with a colorectal anastomosis, functioning anastomosis, 18+years of age, primary surgery/reversal of ileostomy <10 years before recruitment, ileostomy reversed >6 months prior to recruitment

4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41

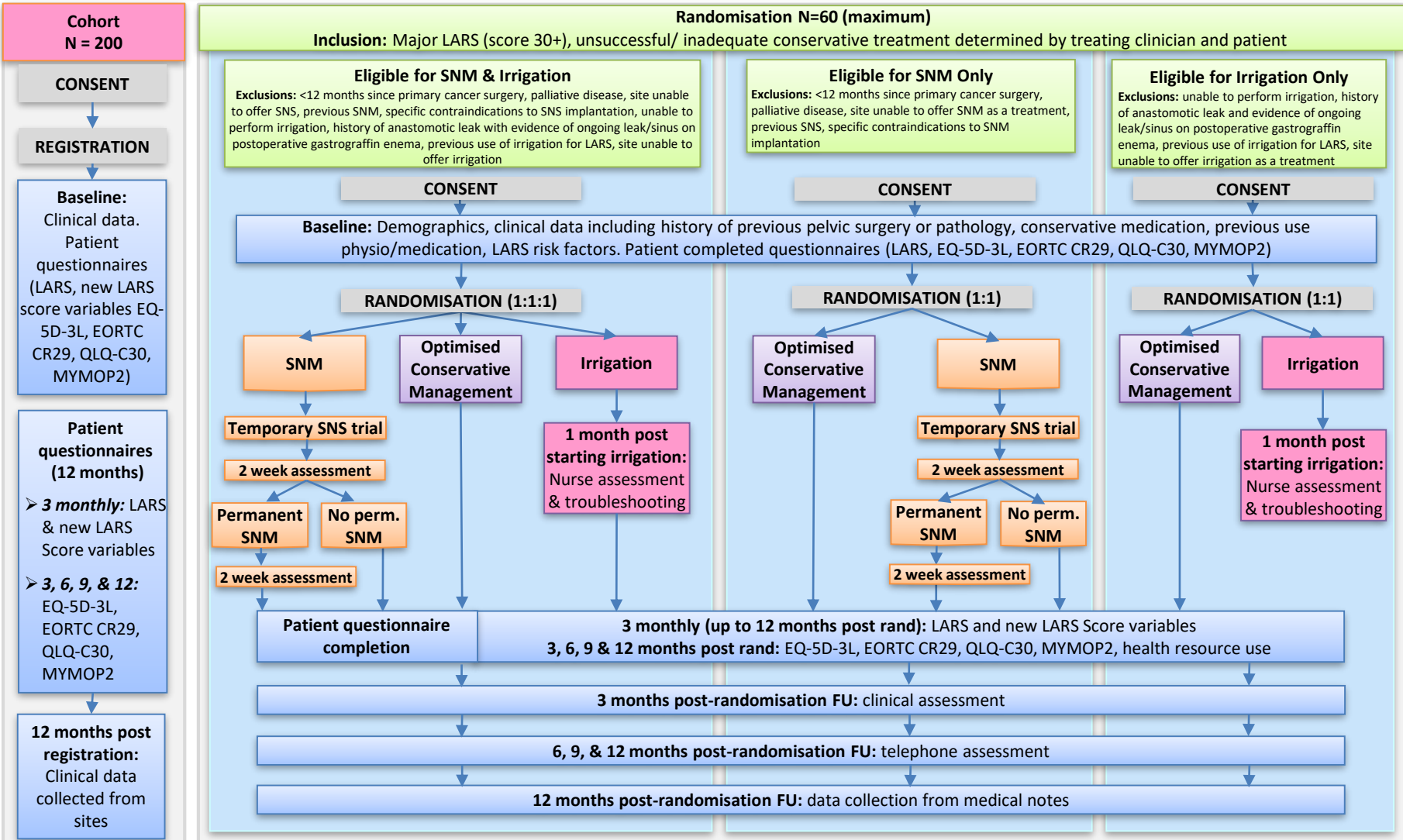


Figure 1: Flow diagram to outline the study design for POLARiS feasibility



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	n/a

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	n/a
	13b	For each group, losses and exclusions after randomisation, together with reasons	n/a
Recruitment	14a	Dates defining the periods of recruitment and follow-up	n/a
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	n/a
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	n/a
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	n/a
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	n/a
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	2
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	n/a
Other information			
Registration	23	Registration number and name of trial registry	1
Protocol	24	Where the full trial protocol can be accessed, if available	9
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

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.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-064248.R1
Article Type:	Protocol
Date Submitted by the Author:	29-Nov-2022
Complete List of Authors:	Coxon-Meggy, Alexandra; Cardiff and Vale University Health Board, Colorectal Surgery; Cardiff University School of Medicine Vogel, Irene; Amsterdam University Medical Centres White, Judith; Cardiff University School of Medicine, Cedar Croft, Julie; University of Leeds, Clinical Trials Research Unit, Leeds Institute of Clinical Trials Corrigan , Neil; University of Leeds Clinical Trials Research Unit Meggy, Alun; Cardiff and Vale University Health Board Stocken, Deborah; University of Leeds Clinical Trials Research Unit Keller, Deborah; Marks Colorectal Surgical Associates Hompes, Roel; Amsterdam University Medical Centre, Department of Surgery Knowles, Charles; Barts and the London SMD, Centre for Academic Surgery Quyn, Aaron; Leeds Teaching Hospitals NHS Trust; University of Leeds School of Medicine Cornish, Julie; Cardiff and Vale University Health Board, Colorectal Surgery
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Gastroenterology and hepatology, Patient-centred medicine, Research methods, Surgery
Keywords:	Colorectal surgery < SURGERY, Clinical trials < THERAPEUTICS, Gastrointestinal tumours < GASTROENTEROLOGY

SCHOLARONE™
Manuscripts

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13

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.

14 Protocol Version 1.1, 07/02/2022

15
16
17
18
19
20
21
22
23

Alexandra H Coxon-Meggy^{1,2} Irene Vogel³, Judith White¹, Julie Croft⁴, Neil Corrigan⁴, Alun Meggy¹, Deborah Stocken⁴, Deborah Keller⁵, Roel Hompes⁶, Charles Knowles⁷, Aaron Quyn^{8,9}, Julie Cornish¹ on behalf of the POLARiS Trial Development Group¹⁰

24
25
26
27
28

Corresponding author: Alexandra Coxon-Meggy
Duthie Ward,
University Hospital of Wales

29
30
31
32
33

Cardiff
CF14 4XW
Telephone: 07534518625
Email: Alexandra.coxon2@wales.nhs.uk

34
35
36
37
38
39

Sponsor: Cardiff and Vale University Health Board,
University Hospital of Wales
Cardiff
CF14 4XW
CAV_Research.Development@wales.nhs.uk

40
41
42

Key Words: rectal cancer, Low Anterior Resection Syndrome, protocol, sacral neuromodulation, transanal irrigation

43
44

Word Count: 3678

45
46
47
48

49 ¹ Cardiff & Vale University Health Board, Cardiff, UK

50 ² Cardiff University School of Medicine, Cardiff, UK

51 ³ Amsterdam University Medical Centres, Department of Surgery, Amsterdam, the Netherlands

52 ⁴ University of Leeds, Clinical Trials Research Unit, Leeds Institute of Clinical Trials, Leeds, UK

53 ⁵ Marks Colorectal Surgical Associates, Lankenau Medical Center, Wyneewood, PA, USA

54 ⁶ Amsterdam Medical Centre, Netherlands

55 ⁷ Barts and the London SMD, Centre for Academic Surgery, Royal London Hospital, Whitechapel, London, UK

56 ⁸ University of Leeds School of Medicine, Leeds, West Yorkshire, UK

57 ⁹ Leeds Teaching Hospitals NHS Trust, Leeds, West Yorkshire, UK

58 ¹⁰ Trial Development Group: Coxon-Meggy AH Vogel I, White J, Croft J, Corrigan N, Meggy A, Hompes R, Keller D, Dale M, Withers K, Jayne D, Warwick A, Ng K-S, Hepburn J, Powell R, Torkington J, Stocken D, Quyn A, Knowles C, Cornish JA

59
60

ABSTRACT

Introduction

Rectal cancer is common with a 60% 5-year survival rate. Treatment usually involves surgery with or without neoadjuvant chemoradiotherapy or adjuvant chemotherapy. Sphincter saving curative treatment can result in debilitating changes to bowel function known as Low Anterior Resection Syndrome (LARS). There are currently no clear guidelines on the management of LARS with only limited evidence for different treatment modalities.

Methods & Analysis

Patients who have undergone an anterior resection for rectal cancer in the last 10 years will be approached for the study. The feasibility trial will take place in 4 centres with a 9-month recruitment window and 12 months follow up period. The primary objective is to assess the feasibility of recruitment to the POLARiS trial which will be achieved through assessment of recruitment, retainment and follow up rates as well as the prevalence of major LARS.

Feasibility outcomes will be analysed descriptively through the estimation of proportions with confidence intervals. Longitudinal patient reported outcome measures (PROMS) will be analysed according to scoring manuals and presented descriptively with reporting graphically over time.

Ethics & Dissemination

Ethical approval has been granted by Wales REC1; Reference 22/WA/0025. The feasibility study is in the process of set up. The results of the feasibility trial will feed into the design of an expanded, international trial.

Trial registration

Trial registered on ClinicalTrials.gov on 08/04/2022. Reference: CT05319054.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This feasibility trial is the first step in addressing a NICE research recommendation to assess the effectiveness of transanal irrigation and sacral neuromodulation in the treatment of major LARS
- The trial is pragmatically designed to optimise and assess recruitment and retainment
- This trial aims to add knowledge on the natural progression of low anterior resection syndrome over time
- This is a feasibility trial and will not be powered to answer whether TAI or SNM is more effective in the treatment of major LARS
- Not all patients with debilitating bowel dysfunction may be identified in the study due to the lack of QoL measures in the current LARS score

INTRODUCTION

Over 10,000 people are diagnosed with rectal cancer each year in the UK (1) with a five-year survival of just over 60%, which has risen by over 35% since the 1970s(2). Whilst the survival rate has vastly improved due to oncological and surgical advances, the adverse consequences of these treatments are now increasingly recognised. One such consequence is Low Anterior Resection Syndrome (LARS) which describes a constellation of bowel dysfunction symptoms including urgency, frequency, faecal incontinence, stool clustering and incomplete evacuation which have a significant impact on quality of life. It is estimated that around 75% of patients who have undergone an anterior resection, the commonest operation for rectal cancer, will be affected by LARS in the first year following surgery(3). Of those patients 25% will have persisting symptoms beyond 1 year, with half having symptoms up to 10 years(4). The severity of LARS is currently calculated using the validated LARS Score which defines LARS as 'no LARS' (score 0-20), minor LARS (score 21-29) and major LARS (score over 30) (5).

LARS was defined in 2012 (6) and whilst it is a widely accepted condition within coloproctology there is limited guidance on management. Patients are often not informed about the likelihood of changes to their bowel function following surgery and the chronicity of these changes (7). Due to the sensitive nature of LARS symptoms there is often a reluctance from patients to discuss their symptoms causing a barrier to treatment and may lead on to a downward spiral with isolation, anxiety and loss of relationships and intimacy(8).

The current treatment for LARS is largely based on that of faecal incontinence (FI), though it is worth noting that FI is only one potential component of LARS. Conservative management treatments including changes to diet, medications such as loperamide and enemas and physiotherapy techniques are the main stay of management. If these do not adequately improve the symptoms of LARS then transanal irrigation (TAI) or sacral neuromodulation (SNM) can be trialled. A recent systematic review looking at the impact of TAI on a range of bowel conditions including LARS suggested improved bowel function and a likely improvement in quality of life (QoL) but a lack of high quality evidence limited the review (9). Currently SNM is only licenced for use in FI, but there is evidence that significant improvements in function might be achieved in patients with LARS as well(10). A systematic review of 21 studies assessing the treatment options for LARS concluded that the existing quality of research was poor with only small studies on single treatments(11). The recent MANUEL project is the first study to address the variability in the treatment of LARS by setting out a clear management pathway (12). The lack of evidence regarding SNM and TAI remains an issue and has led to the National Institute for Clinical Excellence (NICE) identifying this as a research priority the treatment options for LARS (13). The recommendation was to assess effectiveness and safety of SNM and TAI compared to symptomatic treatment for people with major LARS following treatment for colorectal cancer.

The prevalence and natural history of LARS and its treatment strategies remain poorly understood. Clinician and patient awareness and compliance with available treatments remains unknown. The POLARiS trial is designed to further characterise LARS and investigate these specific interventions. Developed in parallel, this feasibility trial will describe the prevalence of LARS and test the POLARiS trial design to explore the feasibility of running a definitive, expanded randomised control trial. The POLARiS feasibility trial will invite individuals who have had an anterior resection, high or low, or a sigmoid colectomy to take part. The inclusion of high anterior resection and sigmoid colectomy participants will aid further characterisation of LARS symptoms in these groups which have been shown to also suffer with bowel dysfunction post-operatively.

OBJECTIVES

The objectives of the feasibility trial are to establish the prevalence of major LARS in patients up to 10 years following treatment for rectal cancer and to explore the study design of the trial prior to commencing an expanded, definitive trial. 3

METHODS AND ANALYSIS

Study Design

This feasibility trial is a multicentre cohort study with embedded randomised controlled trial (RCT) utilising the Trials within in a Cohort (TWiC) study design (14). This feasibility trial is a multi-centre cohort study with embedded open-label, parallel group, randomised control trial, offering two- or three-arm randomisation options depending on eligibility criteria. Participating centres include Cardiff & Vale University Health Board, Leeds Teaching Hospitals NHS Trust, University Hospital Southampton NHS Trust and Aneurin Bevan Health Board. Cardiff & Vale Health Board will act as the trial sponsor. The trial protocol has been developed in line with the 2013 SPIRIT statement(15). The study design is demonstrated in figure 1. The trial will primarily establish the prevalence of LARS in the study sites, and then explore the feasibility to recruit, retain and follow-up patients. All study participants will initially be recruited to the cohort during the 9-month recruitment window. All cohort patients will be asked to complete a LARS score and quality of life questionnaires on recruitment and every 3 months for 12 months. If a participant within the cohort is identified as having major LARS according to their LARS score (score of 30 or more) they will be invited to the RCT. The trial treatments are optimised conservative management (OCM), transanal irrigation (TAI) and sacral neuromodulation (SNM). The trial opened for recruitment on 1st June 2022 and is due to run for 18 months, ending on 1st December 2023.

Study Population

All patients who have had an anterior resection or in the last 10 years will be screened and a random selection of 50 eligible patients per participating site will be approached for this feasibility trial.

Eligibility criteria

Inclusion criteria for the cohort:

- Diagnosis of rectal or sigmoid cancer
- Low or high anterior resection (colorectal resection with anastomosis to the rectum)
- Functioning anastomosis
- 18+ years of age
- Primary surgery/reversal of ileostomy less than 10 years before recruitment
- Reversal of ileostomy at least 12 weeks prior to recruitment with at least a further 12 weeks of standard care to manage symptoms following reversal.
- Willing and able to provide valid informed consent

Exclusion criteria for the cohort:

- Inability to understand and complete study questionnaires independently
 - Due to cognitive or intellectual impairment
 - Due to insufficient English language skills

1
2
3 Patients eligible to join the cohort according to the above criteria will then be screened for eligibility
4 to be randomised.
5

6 Inclusion criteria for the randomised controlled trial (all randomisation options):
7

- 8 • Recruited to cohort study
- 9 • Willing and able to provide valid informed consent for randomisation
- 10 • Major LARS
- 11 ○ Defined as a LARS score of 30 or more
- 12 • Previous unsuccessful conservative treatment as determined by treating clinician and patient

13
14
15 Exclusion criteria for the randomised controlled trial (all randomisation options):
16

- 17 • Pregnancy
- 18 • No previous conservative treatment plan for the management of LARS
- 19 • Does not meet any treatment-specific criteria

20
21 Exclusion criteria for randomised controlled trial TAI-inclusive randomisation options
22 (randomisation options 1 and 3):
23

- 24 • Unable to perform TAI
- 25 • History of anastomotic leak with evidence of ongoing leak/sinus on postoperative
26 gastrograffin enema
- 27 • Previous use of TAI for LARS
- 28 • Site unable to offer TAI as a treatment
- 29 • Any other contraindications advised by the care team, product manufacturer or distributor

30
31
32 Exclusion criteria for SNM-inclusive randomisation options (randomisation options 1 and 2)
33

- 34 • <12 months since primary cancer surgery
- 35 • Palliative disease
- 36 • Site unable to offer SNM as a treatment
- 37 • Previous SNM
- 38 • Specific contraindications to implantation
- 39 • Any other contraindications advised by the care team, product manufacturer or distributor

40 41 42 **Recruitment**

43 Eligible participants will be identified through local cancer databases, note-screening and out-patient
44 clinics at NHS hospital sites. Potential cohort participants will be sent a postal invitation which will
45 include a detailed patient information sheet, reply slip and informed consent form. Participants who
46 have an anterior resection in the last 10 years will be randomly approached. To ensure recruitment
47 targets are met the recruitment log will be regularly reviewed and further participants invited when
48 needed. Participants who are invited but do not respond will receive a follow-up phone call.
49

50 51 52 **Informed Consent**

53 Valid informed consent will be sought in writing from participants prior to enrolment in the study and
54 before any interventions or data collection can take place. Returned consent forms will be checked to
55 ensure completeness and counter signed remotely by a member of the research team.
56

57
58 Participants who are eligible from the cohort, to the RCT will be approached by telephone. Participants
59 will be informed of their eligibility and offered further information about the RCT which will be
60

1
2
3 explained over the phone and followed by a postal patient information sheet. Interested participants
4 will be asked to return a reply slip. On receipt of this an appointment to discuss the trial and sign the
5 consent form will be made in person with a clinically qualified member of the research team.
6
7
8

9 10 **Randomisation**

11 Cohort participants with a LARS score over 30 will be invited to take part in the RCT. Dependent on
12 their eligibility to receive TAI or SNM, patients will be randomised in one of three randomisation
13 options, all with equal allocation ratio. The trial will utilise multiple randomisation options such that
14 ineligibility to one treatment does not exclude a patient from the whole trial.
15
16

17 Randomisation option 1: OCM vs SNM vs TAI

18
19 Randomisation option 2: OCM vs SNM

20
21 Randomisation option 3: OCM vs TAI.
22

23 Randomisation will be carried out by the person consenting the patient to the RCT. Blocked
24 randomisation using variable block sizes will be performed to produce random treatment allocations.
25 An automated 24-hour, online randomisation system will be developed and maintained by the Clinical
26 Trials Research Unit at the University of Leeds. Due to the nature of the interventions, this is a non-
27 blinded trial.
28
29

30 **Interventions**

31 Every patient to be randomised will be given a LARS information booklet which will outline some of
32 the conservative treatments and links to online support. Participants are able to access those
33 treatments and this will be captured on the case report form. Participants who access TAI or SNM
34 outside of the trial will be removed from the study. Participants who wish to stop treatment will be
35 able to do so at their request, a reason for this will be sought.
36
37

38 **Optimised conservative management**

39 The Optimised Conservative Management (OCM) treatment programme has been designed for this
40 feasibility trial using current evidence on the conservative treatment of LARS. The programme will
41 include lifestyle advice, dietary changes, medication and physiotherapy. OCM will be delivered by a
42 suitably qualified healthcare professional with experience in managing bowel dysfunction. All
43 healthcare professionals delivering OCM will undergo training on the POLARiS OCM treatment
44 programme and will be supplied with the guides and patient booklets to use with their patients. Each
45 treatment or management option delivered will be clearly recorded for every participant. The OCM
46 treatments will be tailored to the symptoms and needs of the participant and where available referral
47 on for specialist pelvic floor physiotherapy and dietetics will be encouraged.
48
49
50

51 **Transanal Irrigation**

52 Transanal irrigation (TAI) will be commenced by an appropriately trained clinical nurse specialist. The
53 choice and frequency of TAI, including device, volume and frequency of use, will be guided by clinical
54 expertise and evidence-based guidance(16) and will be recorded for every participant. Participants
55 will undergo a period of training with their TAI device, during which time the device and volume can
56 be changed to achieve optimal outcome for the patient.
57
58
59
60

Sacral Neuromodulation

Participants randomised to SNM will undergo temporary testing according to local protocol (either with temporary testing wire or with the tined lead(17). This testing phase typically lasts one to three weeks and seeks to evaluate acceptability and response (using symptoms diaries) prior to a permanent device being fitted. The temporary and permanent devices will be implanted by a qualified surgeon in sites that can offer SNM.

Assessments

The assessments are carried out at recruitment, and then at 3, 6, 9 and 12 months for cohort and RCT participants. The assessments being used are outlined in table 1 and are to be completed by the participant. These will be used to evaluate the interventions for those participants in the RCT and for LARS characterisation for those in the cohort. Participants who do not return completed questionnaires within one month of them being sent will be followed up in writing or by telephone.

In addition to the study questionnaires each participant will have a case report form completed which will collect further information on participant demographics, medical history and LARS therapies. For randomised participants additional information on their randomisation treatments will also be collected on the case report form.

Table 1 Assessment tools

Assessment/Questionnaire	Description
LARS Score	Internationally validated five question assessment exploring different bowel dysfunction symptoms and their frequency. The overall score (maximum 42) corresponds to either no LARS (0-20), minor LARS (21-29) or major LARS (over 30)(18).
EQ-5D-5L	Designed and validated by Euroqol as a health-related quality of life tool that generates a single index value for health status. This score is also valuable in the assessment of health care evaluation and economic analysis(19).
European Organisation for Research and Treatment of Cancer (EORTC) QLQ-CR29 QLQ-C20	Internationally validated cancer specific questionnaires. The EORTC produce cancer specific quality of life questionnaires (QLQ) which focus on the effects of diagnosis and treatments. The QLQ-C30(20) focusses on cancer whilst the CR29(21) is specific to colorectal cancer.
Measure Yourself Medical Outcomes Profile (MYMOP II)	Patient specific outcome tool in which the patient identifies two symptoms with the most significant impact on their quality of life. This tool allows for an individualised approach and measure regarding the identified symptoms to assess morbidity/adverse events related to treatment and occupational outcomes(22).

Sample Size Estimation

Sample size requirement has been determined in terms of number of patients to be recruited to the cohort and number of site-months of recruitment.

A minimum of 200 patients is the target recruitment set across all investigational research sites in this cohort study. This sample size ensures a maximum 95% confidence interval half-width of 0.058 when estimating proportions in this cohort population, such as the prevalence of major LARS and the

proportions of cohort patients who are eligible for, and recruited to, the RCT. This is sufficiently precise to inform sample size assumptions and expectations in the definitive POLARIS trial.

The aim is to observe a minimum of 36 site-months (4 sites recruiting for 9 months) of recruitment. This will provide sufficient precision of the Poisson parameter estimate of recruitment rate per site per month. With 200 patients recruited to the cohort over 36 site-months, the Poisson parameter estimate would be 5.55 patients recruited per site per month, with a 95% confidence interval half-width of 1.57 i.e. 95% CI: (4.0, 7.1). This is sufficiently precise to inform recruitment rate assumptions and expectations in the POLARIS trial.

We have set a maximum of 60 patients to be recruited to the RCT to allow assessment of acceptability and crossover.

Outcome Measures

The objectives of the trial and the outcome measures those objectives will be assessed against are listed in table 2.

Table 2 Objects and outcome measures

Objectives	Outcome Measures	Endpoints
<p>Primary Objective To assess the feasibility of conducting the 'POLARIS' trial</p>	<ol style="list-style-type: none"> 1) Identify the recruitment rate to the cohort. 2) Assess the characteristics of patients recruited to the cohort. 3) Identify the prevalence of major LARS and onset from time of resection and time of radiotherapy. 4) Identify the eligibility and conversion to recruitment in the RCT including proportions recruited to the three randomisation options. 5) Describe the standard of care and variation across sites. 6) Retention/adherence rate: compliance of patient to the treatment program exploring potential crossover. 7) Follow up rate: willingness to complete and return outcome questionnaires and format of completion. 	<ol style="list-style-type: none"> 1) Baseline, 3 months, 6 months, 9 months 2) Baseline, 3 months, 6 months, 9 months 3) 9 months 4) Baseline, 3 months, 6 months, 9 months 5) 12 months 6) 3 months, 6 months, 9 months, 12 months 7) Baseline, 3 months, 6 months, 9 months, 12 months
<p>Secondary Objectives Clinical and patient reported outcomes</p>	<ol style="list-style-type: none"> 1) Patient reported LARS score, new LARS score variables, EORTC CR29 & QLQ 30, EQ5D and MYMOP II at recruitment and every 3 months 2) Patient reported adverse events 3) Treatments offered, length of treatment, reasons for stopping 	<ol style="list-style-type: none"> 1) Baseline, 3 months, 6 months, 9 months, 12 months 2) Throughout study to 12 months 3) 3 months, 6 months, 9 months, 12 months

A screening log will be kept of all the patients who are invited to take part in the trial. Patients who do not wish to participate in the study will be asked if they would like to provide additional information on why they have declined.

1
2
3 The secondary objective of the trial is to characterise and define the LARS patient population. This will
4 be achieved through longitudinal patient reported outcomes (see Data Collection), specifically
5 calculating the variability (standard deviation) in these measures, in addition to collecting data on the
6 current standard of care offered to patients with bowel dysfunction after anterior resection.
7

8 Adverse events relating to the interventions will be collected and reported in line with Good Clinical
9 Practice. Usability data will be collected for TAI and SNM and analysed along with compliance to
10 treatment and reasons for stopping if applicable.
11
12
13

14 15 **Data Analysis**

16 Feasibility outcomes will be analysed descriptively through the estimation of proportions with
17 confidence intervals (CI). Patient characteristics will be reported descriptively as either proportions
18 (CI) or mean (standard deviation, CI) /median (interquartile range).
19

20
21 Longitudinal PROMs will be scored according to scoring manuals and analysed descriptively and
22 reported graphically over time. Standardised area under the curve will be calculated and reported.
23 Hierarchical repeated measures modelling will include covariate adjustment for stratification factors.
24

25 Randomised treatment groups will be combined across the three randomisation options to describe
26 variability in PROMs for SNM, TAI, OCM.
27

28 As a feasibility trial there will be no statistical testing carried out to compare randomised treatment
29 groups. Rather the variability in measures will inform the statistical design of the definitive trial.
30
31

32 **DATA COLLECTION AND MANAGEMENT**

33 34 **Data Collection**

35 Data collection will be undertaken by an appropriately trained clinical researcher as outlined in the
36 delegation log. Data including basic demographics, medical history and details of their cancer
37 diagnosis and treatment will be collected through health records for all patients recruited to the
38 cohort. A short interview will also be conducted to gather information regarding current and previous
39 treatments they have received for LARS. Participants will be asked to complete the following
40 assessments and questionnaires at recruitment and then every 3 months for 12 months. Assessments
41 can be completed electronically or on paper dependent on patient choice.
42
43
44
45

46 **Data Management**

47 Direct access to data will be granted to authorised representatives from the sponsor and host
48 institution for monitoring and/or audit of the study to ensure compliance with the relevant data
49 protection legislation.
50

51 A combination of paper and electronic data will be collected for this study. All data recorded in paper
52 will be handled, transferred and stored securely. Paper data will be stored in the investigator site file
53 for the duration of the study, in a locked cupboard, in a locked room. Data from paper records will be
54 uploaded digitally by a delegated member of the local research team. Electronic data will be captured
55 using Microsoft forms and/or REDcap. All data collected using third-party software will be stored on
56 NHS PC/servers, or hosted on a secure server in accordance with NHS Information Governance policy.
57 No personal identifiers will be collected on study questionnaires.
58
59
60

Participant's personal details will be stored on a link database, with corresponding ID and NHS number. This database will remain on-site and will be archived in accordance with local electronic data archiving protocols.

Management and safety

The trial will be managed in accordance with the principles of Good Clinical Practice and the UK Policy Framework for Health and Social Care Research. An internal trial management group (TMG) will meet monthly over the duration of the study and its role is to develop the study documentation, determine the study activities and undertake the study activities. The wider TMG will meet every 2-3 months to support the data interpretation and dissemination. The TMG will ensure the study is running to time and that recruitment is on target.

Adverse events (AEs) relating to trial specific interventions will be recorded for the purpose of the study as well as reported to the study Sponsor (Cardiff & Vale University Health Board) and discussed by the TMG, any AEs related to devices will be reported to the Medicines and Healthcare products Regulatory Agency (MHRA) and product manufacturer. The process for reporting AEs is clearly outlined in the study protocol and will be verbally addressed at site initiation visits.

Confidentiality

Data collected during the course of the research will be kept strictly confidential and accessed only by delegated members of the research team. Personal data will not be kept for longer than is required for the purpose for which it has been acquired. All investigators and study site will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018.

PATIENT AND PUBLIC INVOLVEMENT

Two lay representatives were involved in the protocol design and will sit on the Trial Management Group throughout the lifecycle of the trial. The trial protocol and patient related trial documents including the information sheets, consent forms, case report forms and OCM treatment pathway have all been reviewed by the trial's lay representatives.

ETHICS AND DISSEMINATION

The trial will be conducted in accordance to the principles of Good Clinical Practice and the Declaration of Helsinki (2013). This study was reviewed and approved by Wales REC1 (ref: 22/WA/0025).

The outcomes of this feasibility trial will be analysed and adjustments made where necessary to the study design ahead of an expanded, definitive trial. The trial outcomes will also be disseminated to participants upon request and published on completion of the trial in a peer reviewed journal and at international conferences. Authorship for the publication of the results of this study will be based on the principles of the International Committee of Medical Journal Editors Recommendations 2018.

Collaborators

POLARIS feasibility Trial Management Group: Julie Cornish, Aaron Quyn, David Jayne, Charles Knowles, Jared Torkington, Deborah Stocken, Julie Croft, Judith White, Neil Corrigan, Alun Meggy, Alexandra Coxon-Meggy, Irene Vogel, Roel Hompes, Deborah Keller, Andrea Warwick, Kheng-Seong Ng, Julie Hepburn (PPI) & Ralph Powell (PPI).

Contributors

1
2
3 *JC, DK and RH conceived and designed the study. IV & JC secured funding and drafted the initial*
4 *protocol. AHC, JW, JCr, NC, AM, DS, CK, AQ and JC developed the protocol and submitted for*
5 *sponsorship and ethical approval. All authors have had significant input into the production of this*
6 *manuscript.*
7

8 *Funding*

9
10 *This study was funded by Bowel Research UK (charity number 1186061)*

11 *Competing interests*

12
13
14 *Non declared*

15 *Patient consent*

16
17 *Not required.*

18 *Ethics approval*

19
20
21 *Ethical approval for this study has been granted by the Wales Research Ethics Committee.*
22
23
24
25

26 REFERENCES

- 27
28 1. Cancer Research UK. No Title [Internet]. Bowel Cancer Incidence Statistics. 2017. Available
29 from: [https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-](https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/incidence#heading-Zero)
30 [cancer-type/bowel-cancer/incidence#heading-Zero](https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/incidence#heading-Zero)
31
- 32 2. Cancer Research UK. Bowel Cancer Survival Statistics [Internet]. Bowel Cancer Survival
33 Statistics. 2017. Available from: [https://www.cancerresearchuk.org/health-](https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/survival#heading-Zero)
34 [professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/survival#heading-Zero](https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/survival#heading-Zero)
35
- 36 3. Martellucci J, Sturiale A, Bergamini C, Boni L, Cianchi F, Coratti A, et al. Role of transanal
37 irrigation in the treatment of anterior resection syndrome. *Tech Coloproctol* [Internet].
38 2018;22(7):519–27. Available from: <https://doi.org/10.1007/s10151-018-1829-7>
39
- 40 4. Battersby NJ, Bouliotis G, Emmertsen KJ, Juul T, Glynne-Jones R, Branagan G, et al.
41 Development and external validation of a nomogram and online tool to predict bowel
42 dysfunction following restorative rectal cancer resection: the POLARS score. *Gut*. 2018
43 Apr;67(4):688–96.
44
- 45 5. Emmertsen KJ, Laurberg S. Low Anterior Resection Syndrome Score: Development and
46 Validation of a Symptom-Based Scoring System for Bowel Dysfunction After Low Anterior
47 Resection for Rectal Cancer. *Ann Surg* [Internet]. 2012;255(5). Available from:
48 [https://journals.lww.com/annalsurgery/Fulltext/2012/05000/Low_Anterior_Resection_Sy-](https://journals.lww.com/annalsurgery/Fulltext/2012/05000/Low_Anterior_Resection_Syndrome_Score_Development.17.aspx)
49 [ndrome_Score_Development.17.aspx](https://journals.lww.com/annalsurgery/Fulltext/2012/05000/Low_Anterior_Resection_Syndrome_Score_Development.17.aspx)
50
- 51 6. Bryant CLC, Lunniss PJ, Knowles CH, Thaha MA, Chan CLH. Anterior resection syndrome. *Lancet*
52 *Oncol*. 2012 Sep;13(9):e403-8.
53
- 54 7. Ridolfi TJ, Berger N, Ludwig KA. Low Anterior Resection Syndrome: Current Management and
55 Future Directions. *Clin Colon Rectal Surg* [Internet]. 2016 Sep;29(3):239–45. Available from:
56 <https://pubmed.ncbi.nlm.nih.gov/27582649>
57
- 58 8. Kupsch J, Kuhn M, Matzel KE, Zimmer J, Radulova-Mauersberger O, Sims A, et al. To what extent
59 is the low anterior resection syndrome (LARS) associated with quality of life as measured using
60

- 1
2
3 the EORTC C30 and CR38 quality of life questionnaires? *Int J Colorectal Dis* [Internet].
4 2019;34(4):747–62. Available from: <https://doi.org/10.1007/s00384-019-03249-7>
5
- 6 9. Mekhael M, Kristensen HØ, Larsen HM, Juul T, Emmanuel A, Krogh K, et al. Transanal Irrigation
7 for Neurogenic Bowel Disease, Low Anterior Resection Syndrome, Faecal Incontinence and
8 Chronic Constipation: A Systematic Review. *J Clin Med*. 2021 Feb;10(4).
9
- 10 10. Huang Y, Koh CE. Sacral nerve stimulation for bowel dysfunction following low anterior
11 resection: a systematic review and meta-analysis. *Color Dis* [Internet]. 2019 Nov
12 1;21(11):1240–8. Available from: <https://doi.org/10.1111/codi.14690>
13
- 14 11. Dulskas A, Smolskas E, Kildusiene I, Samalavicius NE. Treatment possibilities for low anterior
15 resection syndrome: a review of the literature. *Int J Colorectal Dis* [Internet]. 2018;33(3):251–
16 60. Available from: <https://doi.org/10.1007/s00384-017-2954-x>
17
- 18 12. Christensen P, Im Baeten C, Espín-Basany E, Martellucci J, Nugent KP, Zerbib F, et al.
19 Management guidelines for low anterior resection syndrome - the MANUEL project. *Colorectal*
20 *Dis* [Internet]. 2021/01/24. 2021 Feb;23(2):461–75. Available from:
21 <https://pubmed.ncbi.nlm.nih.gov/33411977>
22
- 23 13. National Institute for Health and Care Excellence [NICE]. *Colorectal Cancer* [Internet]. 2020.
24 Available from: [https://www.nice.org.uk/guidance/ng151/resources/colorectal-cancer-pdf-](https://www.nice.org.uk/guidance/ng151/resources/colorectal-cancer-pdf-66141835244485)
25 [66141835244485](https://www.nice.org.uk/guidance/ng151/resources/colorectal-cancer-pdf-66141835244485)
26
- 27 14. Relton C, Torgerson D, O’Cathain A, Nicholl J. Rethinking pragmatic randomised
28 controlled trials: introducing the cohort multiple randomised controlled
29 trial design. *BMJ* [Internet]. 2010;340. Available from:
30 <https://www.bmj.com/content/340/bmj.c1066>
31
- 32 15. Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013
33 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* [Internet]. 2013;346.
34 Available from: <https://www.bmj.com/content/346/bmj.e7586>
35
- 36 16. Emmanuel A, Collins B, Henderson M, Lewis L, Stackhouse K. Decision Guide for the use of
37 rectal/transanal irrigation in adults [Internet]. MacGregor Healthcare; 2020. Available from:
38 [https://www.macgregorhealthcare.com/wp-content/uploads/2021/05/Decision-](https://www.macgregorhealthcare.com/wp-content/uploads/2021/05/Decision-Guide_2020_UK_new.pdf)
39 [Guide_2020_UK_new.pdf](https://www.macgregorhealthcare.com/wp-content/uploads/2021/05/Decision-Guide_2020_UK_new.pdf)
40
- 41 17. Matzel KE, Chartier-Kastler E, Knowles CH, Lehur PA, Muñoz-Duyos A, Ratto C, et al. Sacral
42 Neuromodulation: Standardized Electrode Placement Technique. *Neuromodulation*. 2017
43 Dec;20(8):816–24.
44
- 45 18. Juul T, Battersby NJ, Christensen P, Janjua AZ, Branagan G, Laurberg S, et al. Validation of the
46 English translation of the low anterior resection syndrome score. *Color Dis Off J Assoc*
47 *Coloproctology Gt Britain Irel*. 2015 Oct;17(10):908–16.
48
- 49 19. NICE. Guide to the methods of technology appraisal 2013 [Internet]. 2013. Available from:
50 <https://www.nice.org.uk/process/pmg9/chapter/foreword>
51
- 52 20. Groenvold M, Klee MC, Sprangers MA, Aaronson NK. Validation of the EORTC QLQ-C30 quality
53 of life questionnaire through combined qualitative and quantitative assessment of patient-
54 observer agreement. *J Clin Epidemiol*. 1997 Apr;50(4):441–50.
55
- 56 21. Whistance R, Conroy T, Chie W-C, Costantini A, Sezer O, Koller M, et al. Clinical and
57 psychometric validation of the EORTC QLQ-CR29 questionnaire module to assess health-
58 related quality of life in patients with colorectal cancer. *Eur J Cancer*. 2009 Sep 1;45:3017–26.
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

22. Measures M. Measure Yourself Medical Outcomes Profile [Internet]. 2021. Available from: <https://www.meaningfulmeasures.co.uk/mymop>

For peer review only

1
2
3 **Figure 1** Flow diagram to outline the study design for POLARiS feasibility.
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

POLARiS: Pathway of Low Anterior Resection Syndrome relief after Surgery feasibility study

BMJ Open

Setting: 4 sites (England & Wales) **Inclusion criteria:** Diagnosed with rectal or sigmoid cancer, left-sided resection with a colorectal anastomosis, functioning anastomosis, 18+years of age, primary surgery/reversal of ileostomy <10 years before recruitment, ileostomy reversed >6 months prior to recruitment

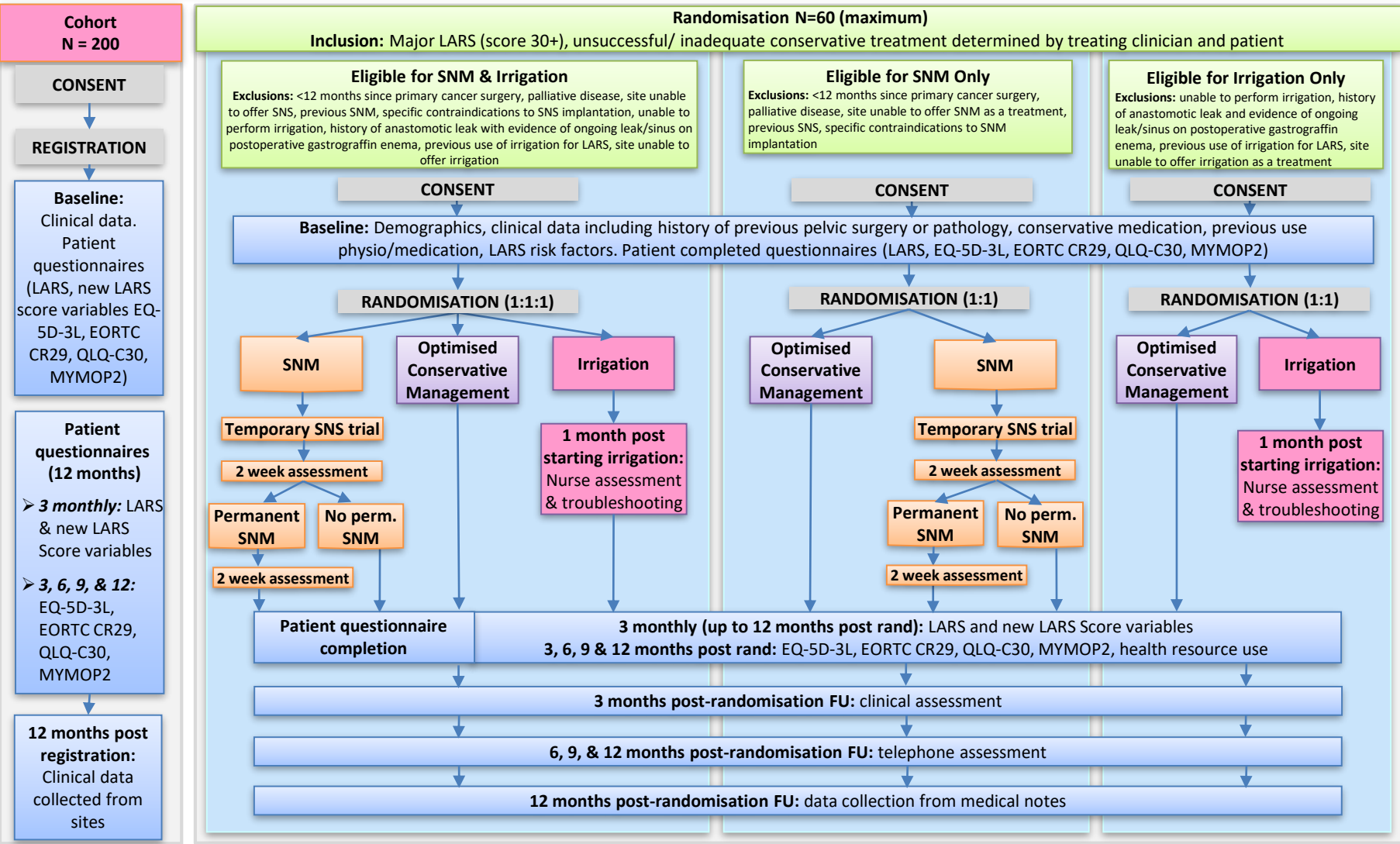


Figure 1: Flow diagram to outline the study design for POLARiS feasibility

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

	Reporting Item	Page Number
Administrative information		
Title	<u>#1</u> Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

1	Trial registration	#2a	Trial identifier and registry name. If not yet	2
2			registered, name of intended registry	
3				
4				
5				
6	Trial registration:	#2b	All items from the World Health Organization Trial	All points
7			Registration Data Set	addressed
8	data set			throughout
9				manuscript
10				
11				
12				
13				
14				
15				
16	Protocol version	#3	Date and version identifier	1
17				
18				
19	Funding	#4	Sources and types of financial, material, and	11
20			other support	
21				
22				
23				
24				
25	Roles and	#5a	Names, affiliations, and roles of protocol	1,11
26			contributors	
27	responsibilities:			
28				
29	contributorship			
30				
31				
32	Roles and	#5b	Name and contact information for the trial	1
33			sponsor	
34	responsibilities:			
35				
36	sponsor contact			
37				
38	information			
39				
40				
41				
42	Roles and	#5c	Role of study sponsor and funders, if any, in	10,11
43			study design; collection, management, analysis,	
44	responsibilities:		and interpretation of data; writing of the report;	
45			and the decision to submit the report for	
46	sponsor and funder		publication, including whether they will have	
47			ultimate authority over any of these activities	
48				
49				
50				
51				
52				
53				
54				
55				
56				
57				
58				
59				
60				

1 Roles and [#5d](#) Composition, roles, and responsibilities of the 10,11
 2
 3 responsibilities:
 4 coordinating centre, steering committee, endpoint
 5 committees
 6 adjudication committee, data management team,
 7
 8 and other individuals or groups overseeing the
 9
 10 trial, if applicable (see Item 21a for data
 11
 12 monitoring committee)
 13
 14

15 Introduction

16
 17
 18
 19 Background and [#6a](#) Description of research question and justification 4
 20
 21 rationale
 22 for undertaking the trial, including summary of
 23 relevant studies (published and unpublished)
 24
 25 examining benefits and harms for each
 26
 27 intervention
 28
 29

30
 31 Background and [#6b](#) Explanation for choice of comparators 4
 32
 33 rationale: choice of
 34
 35 comparators
 36
 37

38 Objectives [#7](#) Specific objectives or hypotheses 5
 39
 40

41 Trial design [#8](#) Description of trial design including type of trial 5
 42
 43 (eg, parallel group, crossover, factorial, single
 44
 45 group), allocation ratio, and framework (eg,
 46
 47 superiority, equivalence, non-inferiority,
 48
 49 exploratory)
 50
 51
 52

53 Methods:

54 Participants,

1 **interventions, and**
 2
 3 **outcomes**

4				
5				
6	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	5
7				
8				
9				
10				
11				
12				
13				
14				
15				
16	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)	5,6
17				
18				
19				
20				
21				
22				
23				
24				
25	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
26				
27	description			
28				
29				
30				
31				
32				
33	Interventions:	#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)	7
34				
35	modifications			
36				
37				
38				
39				
40				
41				
42				
43	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	Study flow diagram (figure 1)
44				
45	adherence			
46				
47				
48				
49				
50				
51				
52				
53	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
54				
55	concomitant care			
56				
57				
58				
59				
60				

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19	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	9
20 21 22 23 24 25 26 27 28 29 30 31	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)	8,9, study flow diagram (figure 1)
32 33 34 35 36 37 38 39 40 41 42 43	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	8
44 45 46 47 48 49	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6

Methods:

Assignment of interventions (for controlled trials)

1	Allocation:	#16a	Method of generating the allocation sequence	7
2				
3	sequence		(eg, computer-generated random numbers), and	
4				
5	generation		list of any factors for stratification. To reduce	
6				
7				
8			predictability of a random sequence, details of	
9				
10			any planned restriction (eg, blocking) should be	
11				
12			provided in a separate document that is	
13				
14				
15			unavailable to those who enrol participants or	
16				
17			assign interventions	
18				
19				
20	Allocation	#16b	Mechanism of implementing the allocation	7
21				
22	concealment		sequence (eg, central telephone; sequentially	
23				
24	mechanism		numbered, opaque, sealed envelopes),	
25				
26				
27			describing any steps to conceal the sequence	
28				
29			until interventions are assigned	
30				
31				
32	Allocation:	#16c	Who will generate the allocation sequence, who	7
33				
34	implementation		will enrol participants, and who will assign	
35				
36			participants to interventions	
37				
38				
39				
40	Blinding (masking)	#17a	Who will be blinded after assignment to	7
41				
42			interventions (eg, trial participants, care	
43				
44			providers, outcome assessors, data analysts),	
45				
46			and how	
47				
48				
49				
50	Blinding (masking):	#17b	If blinded, circumstances under which unblinding	n/a
51				
52	emergency		is permissible, and procedure for revealing a	
53				
54	unblinding		participant's allocated intervention during the trial	
55				
56				
57				
58				
59				
60				

1 **Methods: Data**

2
3 **collection,**

4
5 **management, and**

6
7 **analysis**

8 9			
10			
11	Data collection plan	#18a	Plans for assessment and collection of outcome, 8,10
12			
13			baseline, and other trial data, including any
14			
15			related processes to promote data quality (eg,
16			duplicate measurements, training of assessors)
17			
18			and a description of study instruments (eg,
19			questionnaires, laboratory tests) along with their
20			
21			reliability and validity, if known. Reference to
22			
23			where data collection forms can be found, if not
24			
25			in the protocol
26			
27			
28			
29			
30			
31			
32	Data collection plan:	#18b	Plans to promote participant retention and 8
33			
34	retention		complete follow-up, including list of any outcome
35			data to be collected for participants who
36			discontinue or deviate from intervention protocols
37			
38			
39			
40			
41			
42	Data management	#19	Plans for data entry, coding, security, and 10
43			
44			storage, including any related processes to
45			
46			promote data quality (eg, double data entry;
47			range checks for data values). Reference to
48			
49			where details of data management procedures
50			
51			can be found, if not in the protocol
52			
53			
54			
55			
56			
57			
58			
59			
60			

1	Statistics: outcomes	#20a	Statistical methods for analysing primary and	10
2			secondary outcomes. Reference to where other	
3			details of the statistical analysis plan can be	
4			found, if not in the protocol	
5				
6				
7				
8				
9				
10				
11	Statistics: additional	#20b	Methods for any additional analyses (eg,	n/a
12	analyses		subgroup and adjusted analyses)	
13				
14				
15				
16	Statistics: analysis	#20c	Definition of analysis population relating to	n/a
17	population and		protocol non-adherence (eg, as randomised	
18	missing data		analysis), and any statistical methods to handle	
19			missing data (eg, multiple imputation)	
20				
21				
22				
23				
24				
25				
26	Methods:			
27				
28	Monitoring			
29				
30				
31				
32	Data monitoring:	#21a	Composition of data monitoring committee	10
33	formal committee		(DMC); summary of its role and reporting	
34			structure; statement of whether it is independent	
35			from the sponsor and competing interests; and	
36			reference to where further details about its	
37			charter can be found, if not in the protocol.	
38			Alternatively, an explanation of why a DMC is not	
39			needed	
40				
41				
42				
43				
44				
45				
46				
47				
48				
49				
50				
51	Data monitoring:	#21b	Description of any interim analyses and stopping	10
52	interim analysis		guidelines, including who will have access to	
53			these interim results and make the final decision	
54			to terminate the trial	
55				
56				
57				
58				
59				
60				

1	Harms	#22	Plans for collecting, assessing, reporting, and	10, 11
2			managing solicited and spontaneously reported	
3			adverse events and other unintended effects of	
4			trial interventions or trial conduct	
5				
6				
7				
8				
9				
10				
11	Auditing	#23	Frequency and procedures for auditing trial	10
12			conduct, if any, and whether the process will be	
13			independent from investigators and the sponsor	
14				
15				
16				
17				
18				
19	Ethics and			
20				
21	dissemination			
22				
23				
24	Research ethics	#24	Plans for seeking research ethics committee /	2
25			institutional review board (REC / IRB) approval	
26	approval			
27				
28				
29	Protocol	#25	Plans for communicating important protocol	11
30			modifications (eg, changes to eligibility criteria,	
31	amendments		outcomes, analyses) to relevant parties (eg,	
32			investigators, REC / IRBs, trial participants, trial	
33			registries, journals, regulators)	
34				
35				
36				
37				
38				
39				
40				
41				
42	Consent or assent	#26a	Who will obtain informed consent or assent from	6
43			potential trial participants or authorised	
44			surrogates, and how (see Item 32)	
45				
46				
47				
48				
49	Consent or assent:	#26b	Additional consent provisions for collection and	n/a
50			use of participant data and biological specimens	
51	ancillary studies		in ancillary studies, if applicable	
52				
53				
54				
55				
56				
57				
58				
59				
60				

1	Confidentiality	#27	How personal information about potential and	10, 11
2			enrolled participants will be collected, shared,	
3			and maintained in order to protect confidentiality	
4			before, during, and after the trial	
5				
6				
7				
8				
9				
10				
11	Declaration of	#28	Financial and other competing interests for	11
12	interests		principal investigators for the overall trial and	
13			each study site	
14				
15				
16				
17				
18				
19	Data access	#29	Statement of who will have access to the final	10
20			trial dataset, and disclosure of contractual	
21			agreements that limit such access for	
22			investigators	
23				
24				
25				
26				
27				
28				
29	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care,	n/a
30	trial care		and for compensation to those who suffer harm	
31			from trial participation	
32				
33				
34				
35				
36	Dissemination	#31a	Plans for investigators and sponsor to	10
37	policy: trial results		communicate trial results to participants,	
38			healthcare professionals, the public, and other	
39			relevant groups (eg, via publication, reporting in	
40			results databases, or other data sharing	
41			arrangements), including any publication	
42			restrictions	
43				
44				
45				
46				
47				
48				
49				
50				
51				
52				
53	Dissemination	#31b	Authorship eligibility guidelines and any intended	11
54	policy: authorship		use of professional writers	
55				
56				
57				
58				
59				
60				

1 Dissemination [#31c](#) Plans, if any, for granting public access to the full 11
 2
 3 policy: reproducible protocol, participant-level dataset, and statistical
 4
 5 research code
 6
 7

8 9 Appendices

10
 11
 12 Informed consent [#32](#) Model consent form and other related Supplementary
 13
 14 materials documentation given to participants and material
 15
 16 authorised surrogates
 17
 18

19 Biological [#33](#) Plans for collection, laboratory evaluation, and n/a
 20
 21 specimens storage of biological specimens for genetic or
 22
 23 molecular analysis in the current trial and for
 24
 25 future use in ancillary studies, if applicable
 26
 27
 28

29 None The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative
 30
 31 Commons Attribution License CC-BY-NC. This checklist can be completed online using
 32
 33 <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with
 34
 35 [Penelope.ai](#)
 36
 37
 38
 39
 40
 41
 42
 43
 44
 45
 46
 47
 48
 49
 50
 51
 52
 53
 54
 55
 56
 57
 58
 59
 60