POLARiS: Pathway Of Low Anterior Resection syndrome relief after Surgery

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2 PROTOCOL VERSION

V2.0 29th June 2023	Original approved version
V3.0 5th March 2024	Protocol amendment no. 1: Primary reasons for amendment: • Progression criteria added to the internal pilot section • R1 resection within 24 months added as an SNM specific exclusion • Further detail in relation to temporary SNM assessment • Minor clarifications
V4.0 19th August 2025	Protocol amendment no. 2: Primary reasons for amendment • Extra guidance to collection of non-recruitment data • History of spinal cord stimulator added as a general exclusion criteria • Change to process to identify/approach participants for interviews

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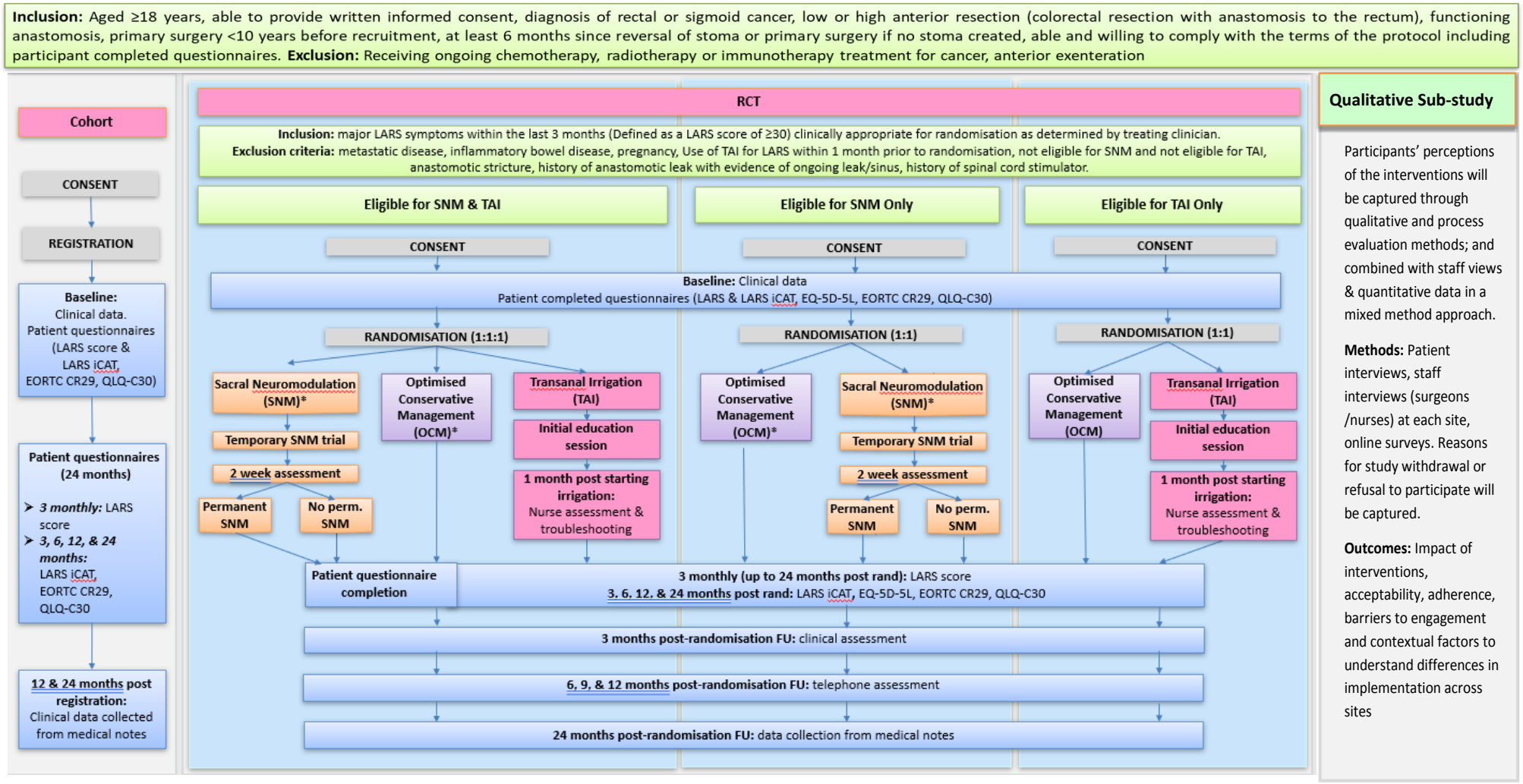
4 TRIAL SUMMARY

Trial Title	POLARiS: Pathway Of Low Anterior Resection syndrome relief after Surgery
Trial Acronym	**POLARiS**
Trial Background	Colorectal cancer is the third most common cancer worldwide with 14,000 patients in the UK being diagnosed with rectal cancer per year. Over half of those patients will undergo major resectional surgery. Low Anterior Resection Syndrome (LARS) is a consequence of this surgery and describes a constellation of bowel symptoms including urgency, faecal incontinence, stool clustering and incomplete evacuation. It has a significant adverse impact on Quality of Life (QoL). LARS symptoms are present in up to 75% of the patients in the first year after surgery and may persist in 25%, remaining in up to half of these patients for more than 10 years. There is poor evidence to support the various treatment options currently in use. As disease-free survival is regarded as the most important factor following curative rectal cancer surgery, QoL and potential ways to improve it may be overlooked. Patients are often not aware or not told that bowel function can change significantly following surgery and radiotherapy and may think any adverse effects will be short-term. It is not known when post-operative bowel dysfunction, which may occur after any colonic resection, can be defined as LARS and how the trajectory of LARS changes over time, especially in patients undergoing radiotherapy.
Trial Design	POLARiS is a prospective, international, open-label, multi-arm, phase 3 randomised superiority trial (RCT) within a cohort (TWiCs design), with internal pilot phase, qualitative sub-study, process evaluation, and economic evaluation.
Trial Aim	**Cohort:** To explore the natural history of LARS, identify predictors of major LARS and to screen patients for recruitment to the RCT **RCT:** To evaluate the clinical and cost-effectiveness of Transanal irrigation (TAI) or Sacral neuromodulation (SNM) versus optimised conservative management (OCM) for people with major LARS.
Trial Endpoints	**Primary Endpoint:** The primary endpoint for the POLARiS RCT is LARS score up to 24 months post-randomisation. The LARS score will be collected at baseline and 3-monthly until 24 months post-randomisation. **Secondary endpoints:** Secondary endpoints include health-related quality of life (EORTC QLQ-C29 and QLQ-C30) up to 24 months post-randomisation/registration, and safety profile (nature and severity of adverse events) within 24 months post-randomisation.
Trial Population:	Approximately 1500 adult participants from UK hospitals and 500 from Australian hospitals who have undergone a high or low anterior resection for colorectal cancer in the last 10 years will be recruited into the cohort. 600 participants from the UK and 200 participants from Australia, with major LARS symptoms, defined as a LARS score of 30+, will be randomised to the randomised controlled trial element.
Randomisation:	Patients entering the RCT will be randomised between Optimised Conservative Management (OCM), Sacral Neuromodulation (SNM) or Trans-Anal Irrigation (TAI). There are three randomisation options all with equal allocation ratios to allow for the

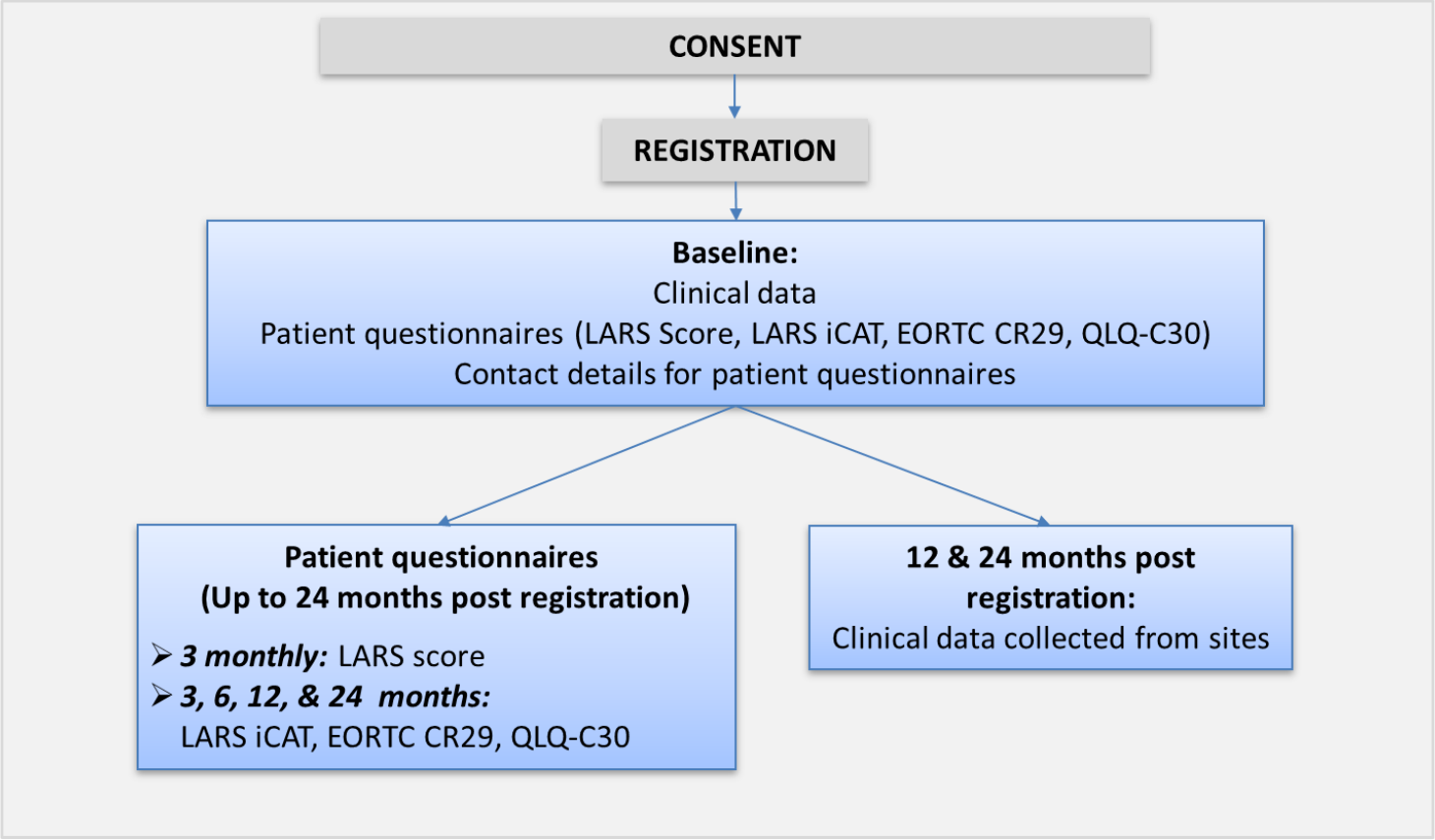
	inclusion of patients who may not be eligible for Sacral Neuromodulation (SNM) or Trans-Anal Irrigation (TAI)
Trial Intervention:	**Optimised Conservative Management (OCM):** The OCM package includes practical support and advice as well as describing treatment options such as diet, medications and physiotherapy. **Sacral Neuromodulation (SNM):** Surgical insertion of a small device that sends electrical pulses to the nerves located in the lower back. This is a two-stage procedure starting with a test phase, whereby a temporary device is implanted. Following a good clinical response, implantation of a permanent battery device is offered. **Trans-Anal Irrigation (TAI):** TAI involves instilling warm water into the rectum and colon via the anus to empty out the stool. Patients attend a one-hour education practical session with a nurse and will be provided with a starter pack.
Duration:	Trial recruitment will be over a 27 month period. Participants will be followed up for 24 months post-registration or post-randomisation.
Evaluation of outcome measures	**Primary outcome measure (RCT and cohort study)** The primary outcome measure for both the cohort study and the RCT is the LARS score. **Secondary outcome measures (RCT and cohort study)** <u>Secondary outcome measures for both the RCT and the cohort study include:</u> • Health-related quality of life and physical, psychological and emotional functioning. • Adverse events **Secondary outcome measures (RCT only)** <u>Secondary outcome measures collected strictly in the RCT include:</u> • Treatment compliance measures • [Outcome(s) used to assess cost-effectiveness] o Cost to the health service of treatment o Modelled long-term costs of health and social care, and broader societal costs • [Occupational outcomes] o Employment status o Time lost from productive activities

5 TRIAL SCHEMA

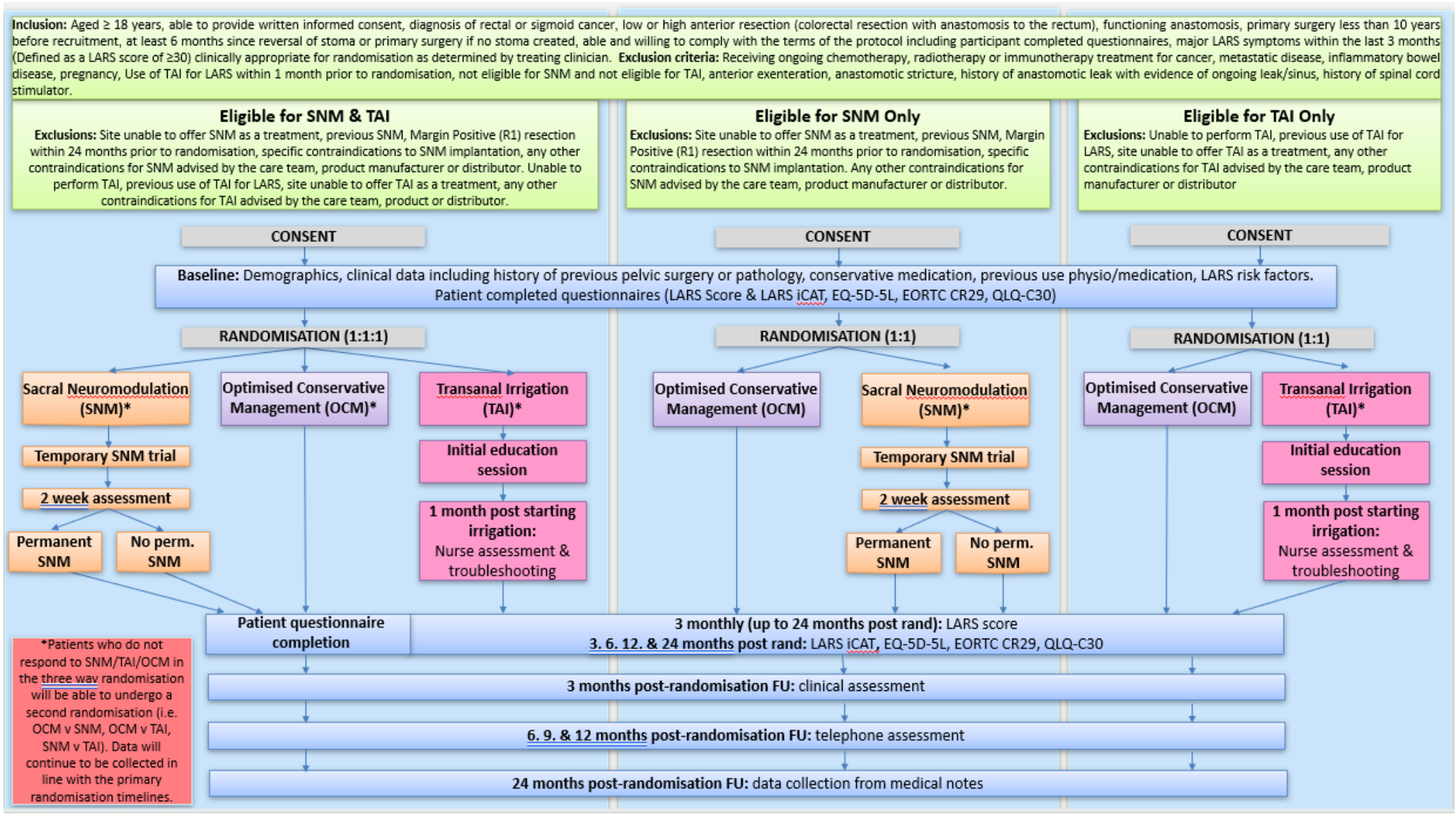


5.1 COHORT SCHEMA

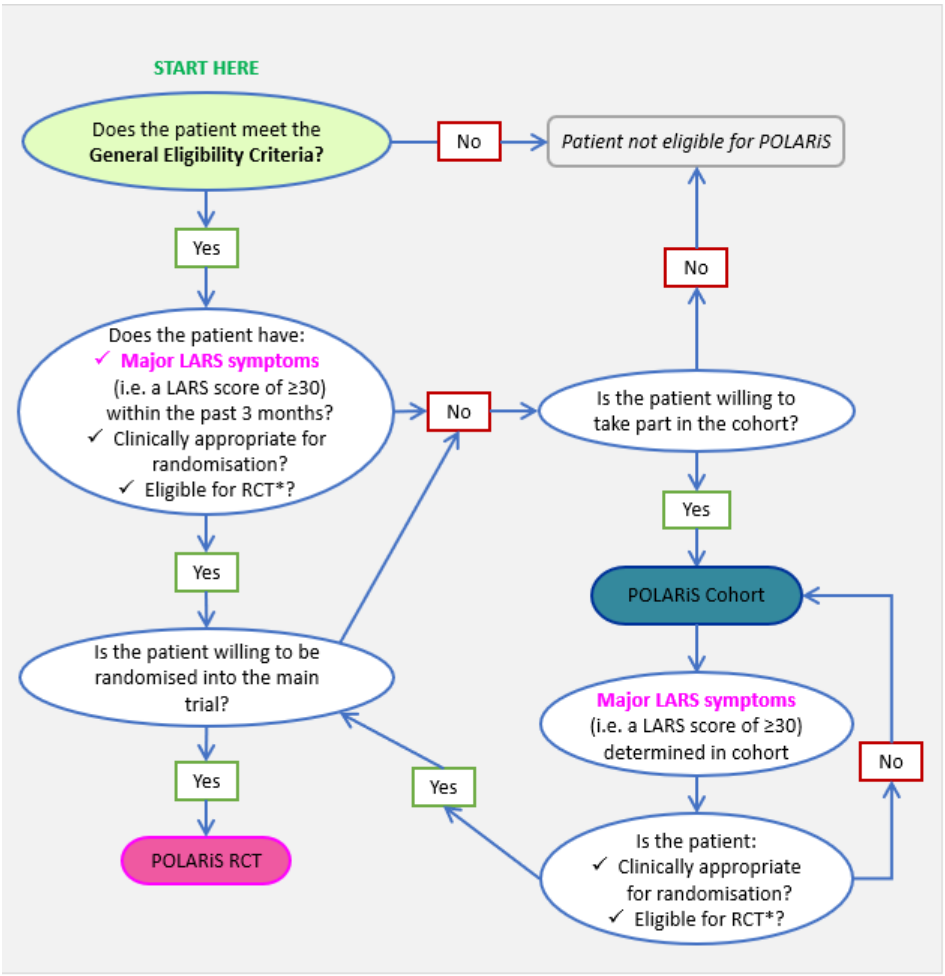
Inclusion criteria: Aged ≥18 years, able to provide written informed consent, diagnosis of rectal or sigmoid cancer, low or high anterior resection (colorectal resection with anastomosis to the rectum), functioning anastomosis, primary surgery <10 years before recruitment, at least 6 months since reversal of stoma or primary surgery if no stoma created, able and willing to comply with the terms of the protocol including participant completed questionnaires
Exclusion: Receiving ongoing chemotherapy, radiotherapy or immunotherapy treatment for cancer, anterior exenteration



5.2 RCT SCHEMA



6 POLARiS Study Entry Decision Tree



POLARiS
Pathway of Low Anterior Resection Syndrome relief after Surgery

General Eligibility criteria

Inclusion:

- ☑ Aged ≥18 years
- ☑ Able to provide written informed consent
- ☑ Diagnosis of rectal or sigmoid cancer
- ☑ Low or high anterior resection (colorectal resection with anastomosis to the rectum)
- ☑ Functioning anastomosis
- ☑ Primary surgery <10 years before recruitment
- ☑ At least 6 months since reversal of stoma or primary surgery if no stoma created
- ☑ Able and willing to comply with the terms of the protocol including participant completed questionnaires

Exclusion

- ☒ Receiving ongoing chemotherapy, radiotherapy or immunotherapy treatment for cancer
- ☒ Anterior exenteration

***Exclusion for RCT**

- ☒ Receiving ongoing chemotherapy, radiotherapy or immunotherapy treatment for cancer
- ☒ Metastatic disease
- ☒ Inflammatory bowel disease
- ☒ Pregnancy
- ☒ Use of TAI for LARS within 1 month prior to randomisation
- ☒ Not eligible for SNM **and** not eligible for TAI
- ☒ Anterior exenteration
- ☒ Anastomotic stricture
- ☒ History of anastomotic leak with evidence of ongoing leak/sinus
- ☒ History of spinal cord stimulator

7 BACKGROUND

7.1 LOW ANTERIOR RESECTION SYNDROME

Colorectal cancer is the third commonest cancer worldwide with 14,000 patients in the UK being diagnosed with rectal cancer per year. Over half of those patients will undergo major resectional surgery. Whilst survival for rectal cancer has improved with advances in surgery and oncology, the adverse consequences of surgery have become increasingly recognised. Low Anterior Resection Syndrome (LARS) is one such consequence and describes a constellation of bowel symptoms after rectal cancer surgery and includes urgency, faecal incontinence, stool clustering and incomplete evacuation. It has a significant adverse impact on Quality of Life (QoL). LARS symptoms are present in up to 75% of the patients in the first year after surgery and may persist in 25%, remaining in up to half of these patients for more than 10 years [1, 2]. Although LARS is common, there is little evidence to support the various treatment options currently in use, with a recent systematic review of 21 studies concluding that the quality of the research was poor for the varying treatment options for LARS [3]. As disease-free survival is regarded as the most important factor following curative rectal cancer surgery, QoL and potential ways to improve it may be overlooked. Patients are often not aware or not told that bowel function can change significantly following surgery and radiotherapy and may think any adverse effects will be short-term [4]. It is not known when post-operative bowel dysfunction, which may occur after any colonic resection, can be defined as LARS and how the trajectory of LARS changes over time, especially in patients undergoing radiotherapy.

7.2 CURRENT MANAGEMENT OF LARS

In general, currently the management of LARS is similar to that of faecal incontinence (FI). The conservative management options include dietary changes, medication and physiotherapy. There is little structured guidance on conservative measurements and a high degree of variability in what different centres can offer. Recommended dietary changes include high-fibre low-fat food, avoidance of wine, cold beverages and spicy or stimulating food. Insoluble fibre may worsen diarrhoea and bloating and as such soluble fibre is better tolerated. Consultation with a specialist dietician may be beneficial for some patients [5]. The medications used in the management of FI and LARS include [3, 6]:

- Loperamide (anti-diarrhoeal) for bowel control.
- Enemas to aid incomplete emptying or to plan defaecation.

Physiotherapy in the form of pelvic floor muscle retraining and biofeedback techniques have been reported to improve symptoms, although only a few, low powered studies have been published [7]. Access to pelvic floor physiotherapy is not available at all hospitals and there is a lack of suitably trained physiotherapists in the UK.

As a result of the lack of clear conservative management guidance, the standard care for major LARS is very variable. For patients suffering with major LARS (defined as a LARS Score of 30 or over), or those who have failed conservative management, treatment options include transanal irrigation (TAI) and Sacral Neuromodulation (SNM).

7.3 EXISTING RESEARCH

There is a lack of published literature regarding the patient journey and symptoms experienced, although it is clear from the studies that are published that LARS significantly impacts on Quality of Life [8-11] . The natural

history of LARS is not understood and whether there is a trajectory from minor to major LARS. LARS is under reported by both patients and clinicians [12].

7.4 Transanal Irrigation (TAI)

Several studies have assessed the efficacy of rectal irrigation on bowel function after low anterior resection, but the sample sizes are small with variable uptake and significant heterogeneity so it is difficult to draw definitive conclusions. The studies to date have focused on high volume irrigation, with little data on low volume irrigation. The most recent study compared high volume irrigation vs control in 45 patients and found a significant improvement in the LARS score at 12 months for TAI (LARS score TAI 22.9 vs control 32.4 P=0.002) [13] . A small RCT compared 18 patients with TAI vs control 3 months after surgery [14]. TAI patients had significantly lower LARS scores compared to control group (LARS 9 vs 31 p=0.001). Martellucci *et al* reported a decrease in LARS score from 35.1 to 12.2 2 ($p<0.0001$) in 27 patients when TAI was used 6 months after restoration of bowel continuity [1]. A retrospective cohort study in the Netherlands showed the mean time between LARS and start of rectal irrigation was 3 years, with 71.6% of patients being continent or only incontinent for flatus after treatment [15]. It is known that there is a wide variation between surgeons in their knowledge of TAI as a treatment option for LARS. A large survey of surgeons in the US & Spain suggest that less than 1/3 would consider TAI as a treatment for LARS [16].

7.5 Sacral Neuromodulation (SNM)

SNM involves the surgical insertion of a small device into the upper buttock which sends electrical impulses to the nerves in the lower back which control bowel and bladder function. SNM is a NICE approved treatment for FI [17]. While not currently commissioned for the treatment of LARS, research suggests comparable success rates in patients with LARS [18]. A recent meta-analysis of 10 studies evaluating SNM in patients with LARS refractory to medical therapy reported an overall median improvement in LARS score of 67% after SNM implantation [19]. A subgroup analysis, including 3 studies with a total of 37 patients, concluded a significant reduction in LARS score (mean difference 17.87, $p<0.001$) after SNM implantation. While these studies show promise, they suffer methodologically from lack of power, and limited generalisability that precludes the wider acceptance of SNM as a treatment option.

7.6 Rationale for POLARiS

With 1 in 4 patients affected by major LARS at one year following surgery and significant impact on QoL, NICE have recognised that treatment of LARS is a research priority. In January 2020 NICE published the following research question: *'What is the effectiveness and safety of sacral neuromodulation and transanal irrigation compared to symptomatic treatment for people with major low anterior resection syndrome?*'. This research priority is based on the lack of evidence supporting the use of TAI or SNM in patients with LARS and complete lack of comparative evidence for different treatments. Another priority is to understand and fill the evidence gap of the symptomatic patient journey leading to major LARS due to it being under recognised and under reported. There is minimal information on the natural history of LARS, with few studies reporting on follow-up beyond 12 months. Understanding this trajectory may allow earlier intervention to prevent or delay the deterioration to the point of major LARS. Is there an optimal time point for the delivery of treatment and does treatment need to be continued ongoing, as there are patients who describe being able to stop TAI after a period of time [20]. POLARiS is a large-scale, complex randomised control trial that will address both of these research priorities.

7.7 POLARiS Feasibility

The POLARiS feasibility study is a separate study being carried out to assess the feasibility of undertaking a large-scale RCT, exploring the acceptability and compliance of trial processes and informing the design of this definitive POLARiS trial[21] .

The main objectives of the feasibility trial are:

- To identify the prevalence of major Low Anterior Resection Syndrome (LARS) within the study population.
- To explore the study design prior to a larger POLARiS trial.

At the time of writing the POLARiS trial protocol, recruitment to the feasibility study is still ongoing. The POLARiS feasibility trial aims to recruit from 4 participating sites. 200 participants will be registered into the cohort and 60 to the RCT element with 15 participants being randomised to SNM, 15 to TAI and 30 to OCM.

8 AIMS AND OBJECTIVES

8.1 Aim

Cohort Aim

To explore the natural history of LARS, identify predictors of major LARS and to screen patients for recruitment to the RCT.

RCT Aim

To evaluate the clinical and cost-effectiveness of Trans-anal irrigation (TAI) or Sacral neuromodulation (SNM) versus optimised conservative management (OCM) for people with major LARS.

8.2 Objectives

Cohort objectives: to describe the natural history of patient reported LARS symptoms and predictors of major LARS.

RCT Primary objectives:

The primary objectives of the RCT are to evaluate the comparative clinical effectiveness of SNM vs OCM and of TAI vs OCM in reducing the severity of LARS in patients who have developed major LARS after having undergone a high or low anterior resection.

RCT Secondary objectives: The secondary objectives of the RCT are to evaluate safety, quality of life and cost effectiveness of SNM vs OCM and of TAI vs OCM in reducing the severity of LARS in patients who have developed major LARS after having undergone a high or low anterior resection.

9 DESIGN

9.1 TRIAL DESIGN

POLARiS is a prospective, international, open-label, multi-arm, phase 3 randomised superiority trial within a cohort (TWiC), with internal pilot phase, qualitative sub-study and economic evaluation.

Patients who have undergone an anterior resection for cancer in the last 10 years, with functional anastomoses will be included in the cohort. Patients with documented major LARS, and patients in the cohort who are identified as having developed major LARS through the study questionnaires, will be invited to enrol in the Randomised Controlled Trial (RCT) within the cohort.

The POLARiS RCT will be conducted as a trial within a cohort (TWiC) [22]. Approximately 1500 participants from UK hospitals and 500 participants from Australian hospitals will be entered into the cohort with the aim to randomise 600 from the UK and 200 from Australia into the RCT.

Patients entering the RCT will have three randomisation options all with equal allocation ratios:

1) Optimised Conservative Management (OCM) vs Sacral Neuromodulation (SNM) vs Trans-Anal Irrigation (TAI)
2) Optimised Conservative Management (OCM) vs Sacral Neuromodulation (SNM)
3) Optimised Conservative Management (OCM) vs Trans-Anal Irrigation (TAI)

These randomisation options correspond to the patient's eligibility, and the site's capacity to deliver, to receive SNM or TAI.

Participants in the cohort and the RCT will be followed up for 24 months. Participants who are entered into the RCT after being identified as developing major LARS from the cohort will continue to be followed up for 24 months from the date of randomisation into the RCT.

Participants who were initially eligible for and randomised via the 3-way randomisation option, may be eligible for a second randomisation (re-randomisation) if they do not respond to their first allocated treatment option – see section 13.4 for details.

The qualitative sub-study will explore the impact of the trial interventions on patients' lives through their own words, and the process evaluation will provide additional context to the RCT study and its interventions (including acceptability, impact and implementation) through mixed methods, see section 26.

9.1.1 INTERNAL PILOT

The trial will include an internal pilot phase, occurring within the first 12 months of open recruitment. The internal pilot will assess patient pathways to cohort recruitment, eligibility for randomisation, conversion from cohort to RCT and compliance to the interventions. The qualitative sub-study and process evaluation (See section 26 and 27) will also inform the internal pilot.

9.1.1.1 Progression Criteria

Progression considerations will be based on review of: i) recruitment, ii) sites, iii) qualitative evaluations.

The progression criteria to expand sites and continue recruitment are informed by Herbert et al [23] based on average recruitment/site/month, numbers of open sites and total recruitment to the Randomised controlled

trial element of the POLARiS study. 'Red/Amber/Green' targets for recruitment and open sites have been set as shown in Table 1 below. The outcome of the internal pilot will be determined by assessment of performance against the progression criteria and graded:

- Green – Trial to continue
- Amber – Explore methods of increasing recruitment and proceed with permission of funder
- Red - Undergo a stopping decision. The decision shall be made by funder

- Each individual criteria will be graded according to the table below, the lowest grade across the categories will determine the overall grade of the pilot outcome..

Table 1: Site and Recruitment Progression Criteria Ranges

Progression Criteria	Red	Amber	Green
RCT recruitment % complete	<73%	73 -99%	100%
RCT Recruitment rate/site/month	<0.67	0.67 – 0.90	≥0.91
Number of sites open	<15	15-19	≥20
Total number of RCT participants recruited	<160	160- 217	≥218

Progression criteria will be reviewed monthly ahead of the 12 months, with projections for progression criteria being discussed with the TMG and TSC. Key areas affecting progression criteria will be identified and targeted for improvement. Findings from interviews and surveys from patients and staff during the internal pilot phase will be fed back from the qualitative research team to the main trial team to troubleshoot emerging issues and to improve the study design. Progression criteria for the qualitative interviews are shown in Table 2 below.

The progression metrics detailed in Table 1 will be used, alongside supplementary data from the pilot phase e.g. screening and treatment compliance data, and findings from the qualitative interviews and process evaluation, to inform the independent committees and funder regarding trial continuation (either unmodified or with a modified protocol).

Table 2: Qualitative Process Evaluation Progression Criteria Ranges

Criteria	Red	Amber	Green
Interviews with RCT participants	<3	3-4	5
Inverviews with Healthcare professionals	<4	4-5	6

9.2 Outcome Measures

Primary outcome measure (RCT and cohort study)

The primary outcome measure for both the cohort study and the RCT is the LARS score[24].

The Low Anterior Resection Syndrome (LARS) Score is a 5 question patient reported measure created in 2012 in Denmark, validated in English language in 2014 [24].

The LARS score is internationally validated as a bowel function assessment following anterior resection. It consists of 5 questions with a score that ranges from 0 to 42 points. The LARS score can be classified into: no

LARS (0-20 points), minor LARS (21-29 points), major LARS (30-42 points). In the analysis, the LARS score will be treated as a continuous variable.

Secondary outcome measures (RCT and cohort study)

Secondary outcome measures for both the RCT and the cohort study are summarised in Table 3 below and include:

- Health-related quality of life and physical, psychological and emotional functioning.
    - EORTC QLQ C30
      Internationally validated, cancer specific quality of life questionnaires. The EORTC questionnaires cover multiple, specified domains including physical and emotional functioning, which will be scored according to the manuals and reported [25].
    - EORTC CR29
      Validated questionnaire module specifically for patients with colorectal cancer [26]
    - LARS iCAT (international consensus assessment tool)
      The LARS iCAT score is being developed to be used with the LARS score. It follows work by Keane C et al [27]. The development of the new LARS iCAT score is being done with the POLARiS study team and the international consensus group. The variables of the LARS iCAT score will be collected as part of this study. This will enable validation of the score and future proofing of the results should the LARS iCAT score come into clinical practice.
- Adverse events (for the definition of adverse events in POLARiS see section 15).

Secondary outcome measures (RCT only)

Secondary outcome measures collected strictly in the RCT include:

- Generic quality of life
    - EQ-5D-5L[28]
      Generic quality of life tool that generates a single utility value for health status for health care evaluation and economic analysis.
- Treatment compliance measures, including:
    - Appointment attendance for planned OCM treatments e.g. physio, dietician.
    - Attendance of education practical session and troubleshooting review for TAI
    - Ongoing consumables for TAI
    - Undergoing planned operation(s) for SNM
- [Outcome(s) used to assess cost-effectiveness]
    - Cost to the health service of treatment
    - Long-term costs of health and social care, and broader societal costs
- [Occupational outcomes]
    - Employment status
    - Time lost from productive activities

Table 3: Summary of secondary outcomes

Outcome	RCT	Cohort study
EORTC C29	☐	☐

EORTC QLQ-C30	☐	☐
EQ-5D-5L	☐	☐
LARS iCAT	☐	☐
Adverse events	☐	☐
Treatment compliance	☐	☐
Cost effectiveness	☐	☐
Occupational outcomes	☐	☐

10 PARTICIPATING SITES

The trial will open in approximately 20 sites in the UK. The trial will also open under a parallel grant in hospitals in Australia, under a separate trial protocol and ethical application. Each site must fulfil a set of pre-specified criteria and complete a form to verify that the site is willing and able to comply with the trial requirements. This will be signed by the proposed local Principal Investigator (PI) on behalf of all staff who will be affiliated with the trial. Research sites will be required to obtain local confirmation of capacity and capability, return all required essential documentation to CTRU, attend a site initiation and OCM training (See section 10.3). Sites should identify a rectal cancer lead and pelvic floor lead.

10.1 Site Eligibility

Participation of sites will be dependent upon the following criteria:

1. Able to offer at least one of the interventions (TAI or SNM)
2. Sites that have access to TAI and an existing Service level agreement (SLA) with a centre offering SNM, still have option for three way randomisation
3. Perform at least 30 High or Low anterior resections for colorectal cancer per year
4. To deliver SNM to trial participants, sites must perform a minimum of 10 SNM (PNE and permanent) procedures per year

Associate PI Scheme: The trial will be registered with the NIHR Associate PI (API) Scheme. APIs must be able to contribute to the trial for at least 6 months. Please contact the CTRU to discuss the inclusion of APIs at sites.

10.2 Intervention Delivery Eligibility

Participating site staff delivering the trial interventions must have the following experience to take part in the trial.

- The person delivering SNM procedures must have performed at least 10 SNM procedures (either temporary or permanent)
- To deliver TAI including delivery of the education session, site staff must have been in the relevant post for at least 3 months
- To deliver/manage OCM, site staff must complete the trial specific OCM training and read the OCM guidance

10.3 Optimised Conservative Management and Current Practice

Participating sites will be assessed for their current standard practise for LARS and treatment options available at their hospital.

To ensure that sites are providing optimised conservative management for participants randomised to OCM, participating sites will be provided with additional training for staff members. This will be in the form of a training presentation, which will be recorded for convenience, and information packs. In addition, patients undergoing OCM will be provided with an OCM patient booklet in addition to a LARS information booklet (online or paper based). All participants randomised to receive a treatment will receive the LARS information booklet.

11 RECRUITMENT SETTING

The cohort will recruit approximately 1500 participants from UK hospitals and 500 from Australian hospitals with approximately 600 UK participants being randomised into the RCT over a period of 27 months from 20 NHS hospitals in the UK. Up to an additional 200 participants will be randomised from 15 Australian hospitals through the NHMRC Clinical Trials Centre, University of Sydney.

11.1 Eligibility Screening

Patients will be identified through cancer databases, note screening, outpatient clinics and in-patients work load at NHS hospital sites, by the direct clinical care team.

Adult patients who have undergone a high or low anterior resection for colorectal cancer (left sided colonic resection with anastomosis to the rectum) in the last 10 years will be eligible for recruitment to the cohort.

Participants should be considered for recruitment to the RCT at the point of screening if they have major LARS (LARS score of 30+) as documented in their medical notes within the last 3 months, or from the longitudinal cohort following a major LARS score. Participants should also have undergone standard management and treatment, still have major LARS and be clinically appropriate to randomise.

Participating research sites will be required to maintain a log of patients, who are considered for participation in the cohort or the RCT but are not recruited because they are ineligible, have major LARS but are not eligible for randomisation, or because they decline participation (in either the cohort or RCT). Participants should be considered for POLARiS if their primary surgery occurred within the last 10 years, they underwent an anterior resection with anastomosis, and are still alive.

Reasons for ineligibility or declining participation will be closely monitored by the CTRU as part of a regular review of recruitment progress. Screening logs should be returned to the CTRU on a quarterly basis. Anonymised information will be collected including:

- Centre
- Time from anterior resection to randomisation (<12 months, 1-5 years, >5 years)
- Age (<50, 50-70, >70)
- Radiotherapy (short course, long course, post-op, none)
- Procedure (HAR/LAR)
- Biological Sex at birth
- Ethnicity
- Deprivation score
- Date screened

- Reason not eligible for participation in the cohort or RCT, or
- Eligible but declined and reason for this, or
- Other reason for non-randomisation

11.2 Informed Consent

Suitability for inclusion will be assessed according to the eligibility criteria and potentially eligible patients will be approached for either the cohort (section 12) or the RCT (sections 13).

Potential participants will be provided with an approved Patient information sheet and informed consent document (PISICD) during standard clinic appointments or by post/email and will have an opportunity to discuss the trial with a suitably qualified member of the direct healthcare team. The PIS will provide detailed information about the rationale, design and personal implications of the trial.

Potential participants will be given as much time as possible (ideally a minimum of 24 hours) to consider the information and to have the opportunity to discuss with family and healthcare professionals before deciding whether or not to take part. The right of the patient to refuse participation without giving reasons must be respected.

Assenting patients will be formally assessed for eligibility and invited to provide informed, written consent for their participation in the cohort or the RCT, including explicit consent for the transfer of a copy of their signed consent form to the CTRU.

Informed consent may only be obtained by the Principal Investigator (PI) or an appropriate, delegated, healthcare professional (RCT and cohort), or appropriately trained and delegated members of the research team (cohort). Anyone who has delegated responsibility to participate in the informed consent process must have knowledge of the trial interventions, have undertaken informed consent training if appropriate, and have received training in the principles of GCP and the Declaration of Helsinki 1996. They must be fully informed of the ethically approved protocol and be authorised and approved by the PI to take informed consent as documented in the trial Authorised Personnel Log (APL). The PI retains overall responsibility for the informed consent of participants at their research site.

The patient consent form with all original signatures must be retained in the Investigator Site File (ISF). A copy of the signed consent form must be given to the participant, and a record of the consent process, detailing the date of consent and witnesses, must also be kept in the participant's medical notes (this may include a copy of the consent form as per local practice). A copy of the signed consent form must also be transferred to the CTRU.

Participants will remain free to withdraw from the trial at any time without giving reasons and without prejudicing any further treatment.

As a result of the TwiCs study design, there are two consent options; consent to the cohort, and consent to the RCT; these 2 options are described in more detail in the relevant sections of the protocol (section 12.2 and section 13.2).

11.3 Concurrent clinical trials

A clinical trial is considered concurrent if the trial procedures occur, or are likely to occur, within the 24-month follow-up period after randomisation to the POLARIS RCT.

Participation in concurrent clinical trials will be considered on a trial-by-trial basis. However, please note that participants will not be eligible for entry into concurrent clinical trials which would preclude delivery of any of

the POLARIS interventions (as defined in section 13.7) that they may receive under their planned randomisation option(s) (see section 13.3.6).

Note that the POLARIS RCT is a pragmatic trial that allows the specifics of the interventions to be at the discretion of those delivering them. Therefore, if a concurrent trial's protocol includes stipulations about how any of the POLARIS intervention(s) must be delivered which would cause treating clinicians to deviate from their usual practice, then a participant from that trial would not be eligible for the POLARIS RCT.

In all cases where enrolment to a concurrent clinical trial is under consideration, please contact the Clinical Trials Research Unit (CTRU, University of Leeds) in the first instance to discuss participant co-enrolment further.

12 POLARiS COHORT

12.1 Cohort Patient Eligibility

Eligibility waivers to inclusion/exclusion criteria are not permitted. Participants must meet all of the inclusion criteria and none of the exclusion criteria for the appropriate eligibility assessment (Cohort or RCT).

Cohort Inclusion criteria

- Aged ≥ 18 years
- Able to provide written informed consent
- Diagnosis of rectal or sigmoid cancer
- Low or high anterior resection (colorectal resection with anastomosis to the rectum)
- Functioning anastomosis
- Primary surgery less than 10 years before recruitment
- At least 6 months since reversal of stoma or primary surgery if no stoma created
- Able and willing to comply with the terms of the protocol including participant completed questionnaires

Cohort Exclusion criteria

- Receiving ongoing chemotherapy, radiotherapy or immunotherapy treatment for cancer
- Anterior exenteration

12.2 Approach and Consent for Cohort

Patients being considered for the cohort element will be provided with a copy of the approved cohort PISICD. Postal/email approach will also include an invitation letter and reply slip with a pre-addressed pre-paid return envelope (postal). Contact details of the research team will be provided should the patient wish for more information. If there has been no response a member of the research team will follow-up by way of a telephone call 2-4 weeks after information provision, to establish whether the patient received the study information and has any questions. Patients may be contacted up to a maximum of 3 times to establish interest in taking part.

Assenting patients will be asked to provide written informed consent for the cohort element only by signing the POLARiS cohort consent form. Signed consent forms returned through the post must also be signed at the research site on receipt of the signed consent form and a copy of the fully signed form provided to the participant. Consent will be taken prior to enrolment into the cohort and before any intervention or data collection can take place. For further details of cohort trial activities see Table 4.

12.3 Timing of consent

Written informed consent should be obtained as close to registration as possible, but must be prior to registration.

12.4 Loss of capacity following informed consent

Loss of mental capacity of a participant after giving informed consent for the trial is expected to be a rare occurrence. Should this eventuality occur, this should be reported to the CTRU by completing the withdrawal eCRF on the POLARiS database **within 7 days** of site becoming aware and no further trial procedures or data collection should occur from this point onwards. Any data collected up to the point of withdrawal will be kept on record and used in the trial analysis.

12.5 Registration to Cohort

12.5.1 Timing of Registration

Registration should take place as soon as possible after consent is obtained. Participants will also be required to complete their baseline participant completed questionnaires as close to registration as possible.

12.5.2 Registration process

All Registrations will be performed centrally using the CTRU automated 24-hour registration/randomisation system, accessed by sites via the CTRU website. Authorised personnel will be provided PIN codes to use alongside their email address to initially access the 24-hour registration/randomisation service. Users will be prompted to create their own passwords the first time they access the 24-hour randomisation system.

Following confirmation of written informed consent and eligibility, participants should be registered into the POLARiS cohort as soon as possible by an authorised member of staff at the research site.

The following information will be required at registration:

- Participant details, including initials and date of birth
- Name and code of the research site
- Name of the person making the randomisation
- Confirmation of eligibility
- Confirmation of written informed consent
- Participant email/mobile phone number (for administration of electronic participant completed questionnaires)

Participants will be allocated a unique 5-digit trial number.

To Register participants to the POLARiS Cohort
visit the web page: https://lictr.leeds.ac.uk/webrand/

After registration complete the participant's contact information on the Contact Form required for quality-of-life administration for participants who have chosen paper QoL completion and send to the CTRU along with

a copy of the consent form. For participants who have chosen electronic QoL completion, email and/or mobile phone number will be collected during the registration process.

Participants GP's must be informed of their patient's participation in POLARiS using the appropriate POLARiS GP letter.

12.6 Schedule of Events

The timings of data collection points and clinical assessments for the cohort are summarised in the table below. Participants are followed up for 24 months.

Table 4: Schedule of Events – Cohort

		Timepoints post-registration						
	Events	**Baseline**	**3 months**	**6 months**	**9 months**	**12 months**	**Continue 3 monthly[3]**	**24 months**
Assessments/ Investigations	**Clinical Assessment**	□[1]				□[2]		□[2]
	Adverse Events					□		□
	Cohort Consent	□						
	Registration	□						
Participant completed questionnaires	**LARS Score**	□	□	□	□	□	□	□
	LARS iCAT	□	□	□		□		□
	EORTC CR29	□	□	□		□		□
	EORTC QLQ-C30	□	□	□		□		□

[1]Face to face or telephone assessment

[2] Later clinical data collection will be collected from medical notes,

[3] LARS score will continue to be completed every 3 months throughout the 24 months follow up period

12.7 COHORT DATA COLLECTION

Participants must be screened, assessed for eligibility and have provided written informed consent before they can be recruited to the cohort (Sections 12.1 and 12.2).

Participants entered into the cohort will undergo an assessment on entry to collect baseline demographic information and details of relevant medical history. Follow up data will be collected from medical notes.

Data collection timepoints for the cohort are shown in Table 5 below.

Table 5: Cohort data collection time points

Study Visit	To be completed	Format and completed by	Data collected (not limited to)
Recruitment (baseline)	Eligibility checklist	Electronic CRF entered by site	Personal details and demographics Relevant medical history including; bowel dysfunction, surgical, oncological and medication history Contact information Participant completed questionnaires
	Baseline Form	Electronic CRF entered by site	
	Registration Form	Electronic CRF entered by site	
	Contact information (paper QoL)	Paper CRF completed by site and sent to CTRU	
	Baseline questionnaires (see section 12.7.1)	**Paper** – given to participant to by site and posted to CTRU **Electronic** – link to online questionnaires administered to participant by CTRU	
12 month post-registration	12 month follow-up Form	Electronic CRF entered by site	Basic demographic data collected from medical notes
24 Month post-registration	24 Month Follow-up Form	Electronic CRF entered by site	Basic demographic data collected from medical notes

Participants will also be asked to complete participant completed questionnaires at baseline and during the follow up period as described in section 12.7.1.

12.7.1 COHORT PARTICIPANT COMPLETED QUESTIONNAIRES

POLARiS participants entered into the Cohort will be asked to complete a set of questionnaires at baseline and at 3-, 6-, 12- and 24-months post-registration. In addition participants will also be asked to complete the LARS questionnaire **every 3 months** throughout the 24 month follow up as shown in Table 4.

The questionnaires include a combination of validated and non-validated questionnaires, utilised to capture participants' medical history, bowel function and quality of life outcomes. The quality-of-life tools included in the cohort are listed below, see section 9.2 for details of the tools.

- LARS Score
- LARS iCAT
- EORTC QLQ-C30 and CR29

Participants will be able to choose whether to complete their questionnaires electronically or on paper.

Baseline questionnaires may be administered to the participants by the research team at the participating site if participants choose to complete on paper, or from the CTRU if participants choose electronic completion.

All follow up questionnaires will be administered to the participants by the CTRU. Participants who choose paper will receive questionnaire packs from the CTRU trial team by post and are asked to return the completed questionnaires to the CTRU using a pre-addressed , pre-paidenvelope. For participants who choose to complete the questionnaires electronically, SMS and/or emails will be sent to the participants from the CTRU with a link to the questionnaire and to prompt completion. A 'thank you' message will be sent to participants by the CTRU upon receipt of a completed questionnaire. If a completed questionnaire is not received at the CTRU by the required time-point, the CTRU will send one reminder to the participant either by post, text or email (depending on the participant's preferences).

Please see section 14 for details on submission of trial data.

12.8 Notification of eligibility for RCT

Participants in the cohort will complete the LARS score questionnaire every 3 months. If a participant records a LARS score of 30 or above, an email notification will be sent to the site notifying them that the participant has major LARS symptoms and should be considered/approached for the RCT. For participants who enter the RCT from the cohort, the cohort follow up schedule will cease and participants will move onto the pathway for the RCT.

12.9 Participant Withdrawal from Cohort

If a participant withdraws after registration, data will continue to be collected from medical notes and CRFs will continue to be completed unless the participant withdraws from any further data collection.

12.10 Pregnancy in Cohort Participants

Any suspected or confirmed pregnancies that occur from the date of registration must be reported to the CTRU using the Notification of pregnancy eCRF on the POLARiS database. Pregnancies in cohort participants can be reported/entered by research sites when completing follow-up data at the standard trial followup timepoints. It is the responsibility of the treating surgeon to decide what course of action should be taken in relation to the participant's ongoing treatment outside of the trial protocol.

13 POLARiS RANDOMISED CONTROLLED TRIAL (RCT)

13.1 PATIENT ELIGIBILITY (RCT)

Eligibility waivers to inclusion/exclusion criteria are not permitted. Participants must meet all of the inclusion criteria and none of the exclusion criteria for the RCT. There are 3 randomisation options for participants recruited to the RCT as described in section 9, and the option will be determined by participants' eligibility for TAI or SNM.

RCT Inclusion criteria

- Aged ≥ 18 years
- Able to provide written informed consent
- Diagnosis of rectal or sigmoid cancer
- Low or high anterior resection (colorectal resection with anastomosis to the rectum)
- Functioning anastomosis
- Primary surgery less than 10 years before recruitment
- At least 6 months since reversal of stoma or primary surgery if no stoma created
- Able and willing to comply with the terms of the protocol including participant completed questionnaires
- Major LARS symptoms within the last 3 months
  - Defined as a LARS score of ≥30
- Clinically appropriate for randomisation as determined by treating clinician

RCT Exclusion criteria:

- Receiving ongoing chemotherapy, radiotherapy or immunotherapy treatment for cancer
- Metastatic disease
- Inflammatory bowel disease
- [1]Pregnancy
- Use of TAI for LARS within 1 month prior to randomisation
- Not eligible for SNM **and** not eligible for TAI
- Anterior exenteration
- Anastomotic stricture
- History of anastomotic leak with evidence of ongoing leak/sinus
- History of spinal cord stimulator

Exclusion criteria for SNM:

- Site unable to offer SNM as a treatment
- Previous SNM
- Margin Positive (R1) resection within 24 months prior to randomisation
- Specific contraindications to implantation
- Any other contraindications advised by the care team, product manufacturer or distributor

Exclusion criteria for TAI:

- Unable to perform TAI
- 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

[1] It is the local sites responsibility to ensure this is assessed in women of child-bearing potential according to local standard of care

13.2 Approach and Consent for RCT

Participants identified as having a major LARS score (i.e. LARS score of 30+) at the point of screening (documented in medical notes within last 3 months) will be provided with an approved PISICD for the randomised trial and will be invited to be randomised to an intervention in the RCT element of the trial. Cohort registration is not required in this scenario.

Participants who have entered into the cohort and are subsequently diagnosed with major LARS (i.e. LARS score of 30+) according to the validated LARS score, can also be invited to be randomised to an intervention in the RCT element.

If a participant records a major LARS score from questionnaire completion in the longitudinal cohort, the CTRU will inform the site via an email notification. The participant will be approached by the research team via a telephone call, where the RCT will be explained. Following the telephone call, participants will be sent the information sheet specific to the randomisation element of the POLARiS study, containing more detailed information about the randomisation process and the treatments they may receive.

Assenting patients will provide written informed consent for the RCT and will be assessed for their eligibility for TAI and SNM. Participants who do not want to be randomised into the RCT, may still remain in/enter the cohort if they wish to, in this case refer to section 12.

13.2.1 Timing of Consent

Written informed consent should be obtained as close to randomisation as possible, but must be prior to randomisation.

Consent for the RCT is a patient-centred and comprehensive process related to the specific treatments the participant is eligible to receive. This is due to the variation in both participants' symptoms and the management systems available to local teams.

13.2.2 Loss of Capacity Following Informed Consent

Loss of mental capacity of a participant after giving informed consent for the trial is expected to be a rare occurrence. Should this eventuality occur, this should be reported to the CTRU by completing the withdrawal eCRF on the POLARiS database **within 7 days** of site becoming aware and no further trial procedures or data collection should occur from this point onwards. Any data collected up to the point of withdrawal will be kept on record and used in the trial analysis.

13.2.3 Approach for Qualitative Sub-Study

Participants who are randomised into the RCT from UK sites will also be offered the opportunity to take part in up to 3 semi-structured interviews spread over the 24 months follow-up period of the study. An expression of interest (EoI) item/slip will be provided as part of the PISICD for the RCT. The EoI will ask for participants' contact information (name, address, telephone, and email) in order that CEDAR qualitative researchers will be able to contact them directly. For more details see section 26.

13.3 RANDOMISATION

13.3.1 TIMING OF RANDOMISATION

Randomisation should take place within 3 months of a documented major LARS score and as soon as possible after consent is obtained. To avoid bias in questionnaires occurring due to patient knowledge of randomisation allocation, baseline participant-completed questionnaires must be completed after the participant has provided written informed consent for the RCT and prior to randomisation.

13.3.2 RANDOMISATION FROM COHORT

Following a major LARS score identified from questionnaire completion in the longitudinal cohort, confirmation of written informed consent and eligibility, participants will be entered into the POLARiS RCT by an authorised member of staff at the research site. Participants will be allocated their randomised intervention and will continue with the same 5-digit trial number that was provided during registration to the cohort. Participants entering from the cohort must complete a set of baseline questionnaires for the randomisation element. Randomisation should take place following completion of the baseline questionnaires.

13.3.3 DIRECT RANDOMISATIONS INTO RCT (DOCUMENTED MAJOR LARS)

Participants with documented major LARS at point of screening can be randomised directly into the RCT element. Following confirmation of written informed consent and eligibility, participants will be entered into the POLARiS RCT by an authorised member of staff at the research site. Participants will be allocated their randomised intervention and a trial number during the randomisation event. Randomisation should take place following completion of the baseline questionnaires.

13.3.4 RANDOMISATION PROCESS

All randomisations (including re-randomisations) will be performed centrally using the CTRU automated 24-hour registration/randomisation system, accessed by sites via the CTRU website. Authorised personnel will be provided PIN codes to use alongside their email address to initially access the 24-hour registration/randomisation service. Users will be prompted to create their own passwords the first time they access the 24-hour randomisation system.

To allow for electronic completion of baseline questionnaires, there is a 2 step randomisation process (pre-randomisation and randomisation). Both steps are completed via the CTRU automated 24-hour registration/randomisation system.

The following information will be required at pre-randomisation and/or randomisation:

- Participant details, including initials and date of birth
- Name and code of the research site
- Name of the person making the randomisation
- Confirmation of eligibility
- Confirmation of written informed consent
- Cohort Trial Number if applicable
- Participant's Email address/mobile phone number (for administration of electronic participant completed questionnaires)
- Randomisation option (see section 13.3.6)

- Stratification factors (see section 13.3.6)

To randomise participants to the POLARiS RCT
visit the web page: https://lictr.leeds.ac.uk/webrand/

After randomisation, complete the participant's contact information on the Contact Form (for participants who have chosen paper QoL completion) required for quality-of-life administration and send to the CTRU along with a copy of the consent form. For participants who have chosen electronic QoL completion, email and/or mobile phone number will be collected during the randomisation process.

Participants' GPs must be informed of their patient's participation in POLARiS using the appropriate POLARiS GP letter.

13.3.5 LARS Information Booklet

The LARS information booklet is a detailed support document for patients identified as having major LARS and was developed specifically for use in the POLARiS trial. The booklet aims to inform and advise patients regarding their condition. The booklet includes practical support and advice that can be implemented independently to alleviate or control their symptoms, as well as providing information on available medical treatments.

All participants enrolled into the RCT should be given the LARS information booklet when they are randomised to the trial.

13.3.6 Treatment allocation (RCT)

Participants who enter the RCT will be randomised between OCM, TAI or SNM. There are 3 randomisation options as shown below, all with equal ratios.

1. OCM vs SNM vs TAI
2. OCM vs SNM
3. OCM vs TAI

Each randomisation option will be carried out using a computer-generated minimisation programme incorporating a random element to ensure treatment groups are well-balanced for the following participant characteristics, details of which will be required for randomisation:

- Centre
- Time from anterior resection to randomisation (<12 months, 1-5 years, >5 years)
- Biological Sex at birth
- Age (<50, 50-70, >70)
- Radiotherapy (short course, long course, post-op, none)
- Procedure (HAR, LAR)

At the end of the Randomisation event, participants will be allocated a treatment option and a unique 5-digit trial number (for a direct randomisation). Participants recruited from the cohort will retain the same trial number.

13.4 Second Randomisation

Participants who were initially eligible for and randomised via the 3-way randomisation option, may be eligible for a second randomisation (re-randomisation) if they do not respond to their first allocated treatment option. See Table 6 below for re-randomisation guidance. For participants who undergo a second randomisation, data will continue to be collected in line with the primary randomisation timelines.

Table 6 Criteria for re-randomisation depending in initial allocation

Initial allocation	Criteria for re-randomisation	Second Randomisation eligible for
OCM	• Major LARS after at least 12 weeks after initiation of OCM treatment • Clinician/participant agrees OCM has failed and suitable for re-randomisation	*TAI vs *SNM
TAI	• Major LARS after at least 12 weeks from TAI education session • Participant agrees to stop TAI and be re-randomised	OCM vs *SNM
SNM	• Temporary SNM considered to be unsuccessful and still major LARS score • 2 weeks post removal of temp SNM device OR • Permanent SNM considered to be unsuccessful after 6 months • Post removal of permanent SNM device • Patient agrees to be re-randomised	OCM vs *TAI

*Participants must be confirmed as eligible according to the relevant treatment eligibility at the point of a second randomisation. For treatment specific eligibility see section 13.1

The following information will be required to perform the second randomisation:

- Participant details, including initials and date of birth and Trial Number
- Name and code of the research site
- Name of the person making the randomisation
- Confirmation of eligibility and randomisation option eligible for
- Stratification factors
    - Time from anterior resection to randomisation (<12 months, 1-5 years, >5 years)
    - Age (<50, 50-70, >70)

To perform a second Randomisation for a POLARiS participant

visit the web page: https://lictr.leeds.ac.uk/webrand/

13.5 RCT SCHEDULE

Table 7: Schedule of Events - RCT OCM

		Trial Time points (post-randomisation)						
	Events	**Baseline[1]**	**3 months**	**6 months**	**9 months**	**12 months**	**Continue 3 monthly[2]**	**24 months**
Assessments/ Investigations	**Consent**	□						
	Randomisation	□						
	Clinical Assessment	□	□					
	Telephone Assessment			□	□	□		
	Clinical Data Collection (medical notes)							□
	Adverse Events		□	□	□	□		□
Participant completed questionnaires	**LARS Questionnaire**	□	□	□	□	□	□	□
	LARS iCAT	□	□	□		□		□
	EQ-5D-5L	□	□	□		□		□
	EORTC CR29	□	□	□		□		□
	EORTC QLQ-C30	□	□	□		□		□
	Health Resource Use	□	□	□		□		□
Qualitative[4]	**Interview**	□[3]	□					□
	Survey		□					□

[1]Baseline participant completed questionnaires should be completed after consent but before randomisation
[2] LARS score will continue to be completed every 3 months throughout the 24 months follow up period
[3] Up to 6 weeks from randomisation
[4]A sub-set of participants only will take part in the qualitative sub-study interviews and surveys

Table 8: Schedule of Events - RCT TAI

tions	Events	Trial Time points (post-randomisation)										ths
	Events	Baseline[1]	Operative (temporary SNM)	2-week post-operative review	Operative (permanent SNM)	3 months	6 months	9 months	12 months	Continue 3 monthly[2]	24 months	
Assessments/ Investigations	Consent	□	□			□						
	Randomisation	□	□									
	Clinical Assessment	□	□	□	□	□						
	Telephone Assessment						□	□	□			
	Clinical Data Collection (medical notes)										□	□
	Adverse Events	□	□	□	□	□	□	□	□		□	
Participant completed questionnaires	LARS Questionnaire	□	□	□		□	□	□	□	□	□	□
	LARS iCAT	□	□			□	□		□		□	□
	EQ-5D-5L	□	□			□	□		□		□	□
	EORTC CR29	□	□			□	□		□		□	□
	EORTC QLQ-C30	□	□			□	□		□		□	□
	Health Resource Use	□	□			□	□		□		□	□
Qualitative[4]	Interview	□[3]	□[3]			□					□	□
	Survey					□					□	□

[1]Baseline participant completed questionnaires should be completed after consent but before randomisation
[2] LARS score will continue to be completed every 3 months throughout the 24 months follow up period
[3] Up to 6 weeks from randomisation
[4]A sub-set of participants only will take part in the qualitative sub-study interviews and surveys

13.6 Baseline/Pre-Treatment Investigations and Preparation

All participants enrolled in the RCT will be required to undertake a baseline assessment upon study entry with a member of the research team. Baseline demographics and details of relevant medical history will be collected.

All participants randomised to a treatment arm in the RCT will also attend a consultation to undergo training with an appropriately qualified healthcare professional for the intervention they were randomised to:

- Participants undergoing TAI will attend a one-hour practical education session with a specialist nurse where the device and volume will be decided.
- Participants randomised to SNM will have a consultation with their local clinician performing the SNM procedure.
- Participants in the OCM group will have a consultation with a clinical member of the study team where appropriate treatments will be instigated.

Pre-treatment investigation and preparation will be as per institutional protocol. For participants randomised to receive SNM this may include:

- Anorectal Physiology
- Endoanal ultrasound

13.7 Intervention Details (RCT)

All interventions used in this study are NICE approved treatments of faecal incontinence, are CE and/or UKCA marked and being used within their licensing specification.

13.7.1 Transanal Irrigation

TAI involves instilling warm water into the rectum and colon via the anus to empty out the stool. There are several commercially available TAI systems and broadly, systems can be divided into low and high volume (the former is slightly cheaper, easier to use and less invasive than the latter). TAI can be delivered via a variety of different systems. The choice of system will be individual to the patient and their requirements and ability to tolerate the irrigation. Each site will be responsible for the procurement of irrigation systems used for their patients. The choice of the system will be determined by the medical practitioner. All irrigation products will be CE/UKCA marked and approved for local use.

Treatment involves a one-hour education practical session with a nurse and participants will be provided with a starter pack. Participants will have a follow up/troubleshooting review 2-4 weeks after the education session.

13.7.2 Sacral Neuromodulation

SNM involves surgical insertion of a small device that sends electrical pulses to the nerves located in the lower back. The SNM electrodes can be inserted into the S3/S4 sacral foramen and connected to a subcutaneous pulse generator.

SNM implantation will be performed in accordance with each research site's usual practice and will include up to two x-rays to ensure the electrodes are in the correct position. SNM implantation is a two-stage procedure. A

temporary device is implanted and the degree of response to the device is recorded by the participant over the course of one to three weeks.

The assessment of response is at the discretion of the local clinical team. If the response is negative, the temporary device is removed. If the patient demonstrates an appropriate neurophysiological response to percutaneous nerve evaluation (S3/S4 motor or sensory response) and a subjective improvement in symptoms of LARS during a trial of stimulation', they should be offered implantation of a permanent battery device.

Both procedures are performed as day-cases. Post-operative care will be as per standard practice but participants must be reviewed for the trial according to the trial follow up schedule (section 13.7.4).

There are different SNM devices available for clinical use with rechargeable and non-rechargeable battery options for the permanent device. The decision of which SNM device is used, and whether to use a temporary wire electrode or the tined quadripolar electrode lead for the test phase will be at the discretion of the clinical team/patient.

13.7.3 Optimised Conservative Management

Site staff will receive education around OCM and a suggested algorithm of management based on best available evidence/guidance.

Sites will be trained to deliver the OCM to the standard expected from the trial through Site Initiation Visits, presentations, videos and guidance manuals.

The OCM package has been designed by experts in the area of pelvic floor and LARS based on current evidence and the findings of the recent MANUEL report [29]. All aspects of the OCM package have also been reviewed by PPI representatives. The OCM package includes practical support and advice as well as describing treatment options such as diet, medications and physiotherapy. Participants' OCM treatment plan will be discussed during their initial consultation as soon as possible following randomisation, which may be at the same visit as randomisation. Further management and advice will be offered during the 3-month post randomisation visit.

The OCM package will include:

- A discussion regarding medication options
- Completion of food diary
- Bespoke pelvic floor physiotherapy programme (if available at site)
- Dietician review (if available at site)

To determine success of the OCM, participants must continue their tailored treatment package for at least 1 month, or course of pelvic floor physiotherapy if this is available (typically 2-3 sessions over 12 week period).

13.7.4 RCT Follow up

RCT participants will be followed up for 24 months from the date of randomisation. Participants who were identified from the longitudinal cohort will be followed up for 24 months from the date of randomisation according to the RCT follow up pathway and the cohort follow up schedule will cease.

Participants will be reviewed at the following time points.

- *TAI arm only:* 1-month post-irrigation education session: Nurse assessment and troubleshooting
- *SNM arm only:* 2 weeks post temporary SNM LARS Assessment

- 3 months post-randomisation (clinical assessment)
- 6 months post-randomisation (telephone assessment)
- 9 months post-randomisation (telephone assessment)
- 12 months post-randomisation (telephone assessment)
- 24 months post-randomisation (data collected from medical notes)

13.8 RCT Data collection

Participants must be screened, assessed for eligibility and have provided written informed consent before they can then be recruited to the RCT.

All participants will be reviewed in clinic at 3 months post-randomisation and undergo telephone assessments at 6, 9 and 12 months. Data will also be collected from participant medical notes at 24 months post-randomisation.

Participants randomised to TAI will attend a trouble shooting appointment at 1 month after starting irrigation and participants randomised to SNM will attend a 2 week review after implantation of the temporary device.

Data collection timepoints for the RCT are shown in Table 10 below.

Table 10 RCT data collection time points

Study Visit	To be completed	Format and completed by
Recruitment (baseline)	Eligibility checklist	Electronic CRF entered by site
	Baseline Form	Electronic CRF entered by site
	Randomisation Form	Electronic CRF entered by site
	LARS information booklet	Paper/Electronic copy given to randomised participants by site
	OCM participant booklet	Paper/Electronic copy given to participants randomised to OCM. Given to participants by site
	Contact information (paper QoL)	Paper CRF completed by site and sent to CTRU
	Baseline questionnaires (see section 40)	**Paper** – given to participant to by site and posted to CTRU **Electronic** – link to online questionnaires administered to participant by CTRU
Operation (SNM only)	SNM and Operative Details	Electronic CRF entered by site
3 Month post-randomisation	3 Month Follow-up (Clinic assessment)	Electronic CRF entered by site
6 Month post-randomisation	6 Month Follow-up (telephone assessment)	Electronic CRF entered by site

9 Month post-randomisation	9 Month Follow-up (telephone assessment)	Electronic CRF entered by site
12 month post-randomisation	12 month follow-up Form (telephone assessment)	Electronic CRF entered by site
24 Month post-randomisation	24 Month Follow-up Form (medical notes)	Electronic CRF entered by site

13.8.1 PRE-TREATMENT DATA COLLECTION

Data collected on the pre-treatment CRFs (Eligibility Checklist, Baseline, and Randomisation Forms) will include (but will not be limited to):

- Personal details, demographics including height, weight, gender, and American Society of Anesthesiologists (ASA) grade (I, II, III) and deprivation score
- Relevant medical history including bowel dysfunction, surgical, oncological and medication history
- Details of pre-treatment/pre-operative investigations
- Details of anastomosis
- LARS symptoms
- Previous treatments
- Other information to confirm eligibility

Following written informed consent, participants will also be asked to complete the baseline participant-completed questionnaires. For participants in the RCT, these should be completed prior to randomisation wherever possible (where this is not possible this must be prior to the participant being made aware of their randomised treatment).

13.8.2 TREATMENT DATA COLLECTION

13.8.2.1 Operative Data Collection (SNM Participants)

Participants randomised to SNM will undergo implantation of a temporary SNM device and will attend a 2 week review after implantation of the temporary device. Insertion of a permanent device will depend on the success of the temporary device.

Operative data will be collected on the SNM participants relating to the operation(s) including (but not limited to):

- Surgeon
- Performed operation (temporary or permanent)
- Duration of operation
- Device details
- Lead details for test phase (temporary wire electrode or tined quadripolar electrode)
- Use of X-ray

- Local +/- sedation or general anaesthetic for insertion
- Site lead placed
- Number of leads placed
- Final amplitude of device
- Program started on
- Location stimulation felt
- Any intra-operative complications, including device-related complications

13.8.2.2 TAI Data Collection

Participants randomised to TAI will attend an initial educational session followed by a trouble shooting appointment 2-4 weeks after starting irrigation, data will be collected including (but not limited to):

- Education session details
- Device details
- Volume of irrigation
- Frequency of irrigation
- Side effects or problems
- Details of trouble shooting appointment

13.8.2.3 OCM Data Collection

Participants randomised to the OCM arm may receive advice or attend appointments to discuss medication advice, dietary advice and physiotherapy. Data detailing the participant's OCM package will be collected.

13.8.3 Follow-Up Data Collection

All participants will be reviewed in clinic at 3 months post-randomisation and undergo telephone assessments at 6, 9 and 12 months. Data will also be collected from participant medical notes at 24 months post-randomisation.

Data collected during the follow up period will include (but not limited to):

All participants

- Treatment and device details and changes
- LARS score and symptoms
- Adverse events
- Treatment failures and reasons for failure
- Changes in medication (medications, doses, frequency)
- Adjuncts
- Visit attendance

SNM

- Lead/pocket revisions
- Decision to move to permanent SNM device or not and reasons (LARS, patient diary)
- Battery details

TAI

- Number of catheters used
- Volume of water used (average)
- Devices used and frequency of use (on average)
- Number of any additional visits and duration
- Ongoing consumables

OCM

- Medication details
- Diet details (and if formal dietician referral)
- Adjuncts used (ie anal inserts)
- Physiotherapy details (if applicable) including treatments used, number of visits and duration

13.8.4 PARTICIPANT COMPLETED QUESTIONNAIRES (RCT)

POLARiS participants entered into the RCT will be asked to complete a set of questionnaires at baseline and at 3-, 6-, 12- and 24-months post-randomisation, in addition participants will also be asked to complete the LARS questionnaire every 3 months throughout the 24 month follow up as shown in Table 7 to Table 9.

Table 9The questionnaires include a combination of validated and non-validated questionnaires, utilised to capture participants' medical history, bowel function and quality of life outcomes and a health resource use questionnaire for the health economics assessment. The quality-of-life tools included in the RCT are listed below, refer to section 9.2 for details of the tools.

- LARS Score
- LARS iCAT
- EQ-5D-5L
- EORTC QLQ-C30 and CR29
- Health Resource Use

Participants will be able to choose whether to complete their questionnaires electronically or on paper.

Baseline questionnaires may be administered to the participants by the research team at the participating site if participants choose to complete on paper, or from the CTRU (following pre-randomisation) if participants choose electronic completion.

All follow up questionnaires will be administered to the participants by the CTRU. Participants who choose paper completion will receive questionnaire packs from the CTRU trial team by post and are asked to return the completed questionnaires to the CTRU using a pre-addressed, pre-paid envelope. For participants who choose to complete the questionnaires electronically SMS and/or emails will be sent to the participants from the CTRU with a link to the questionnaire and to prompt completion. A 'thank you' message will be sent to participants by the CTRU upon receipt of a completed questionnaire. If a completed questionnaire is not received at the CTRU by the required time-point, the CTRU will send one reminder to the participant either by post, text or email (depending on the participant's preferences).

13.9 Pregnancy (RCT)

Pregnant participants are not eligible for the RCT element due to contraindication with TAI and SNM. Any suspected or confirmed pregnancies that occur from the date of randomisation must be reported to the CTRU using the Notification of pregnancy eCRF on the POLARiS database **within 7 days** of the research site becoming aware. All further trial mandated treatment must be stopped immediately if a pregnancy occurs or is suspected during this time; it is the responsibility of the treating surgeon to decide what course of action should be taken in relation to ensuring the participant's ongoing treatment outside of the trial protocol.

The CTRU will inform the Sponsor of all reported pregnancies in the RCT.

13.10 Participant withdrawal from RCT

In line with usual clinical care, cessation or alteration of treatment at any time will be at the discretion of the attending clinician or the participant themselves.

If a participant refuses to undergo their randomised intervention, standard NHS treatment as offered in the local Health Board or Trust will be offered.

If a participant withdraws after randomisation participants will still attend for follow-up assessments unless unwilling to do so, and CRFs will continue to be completed.

The PI, or delegate, should make every effort to ensure that the specific wishes of any participant who wishes to withdraw consent to further involvement in the trial are defined and documented using the withdrawal eCRF on the POLARiS database **within 7 days** of the withdrawal request. This is to ensure that the correct processes are followed by the CTRU and research site following the withdrawal of consent.

Receipt of a withdrawal form will stop the process of a notification of participant questionnaires to participants if applicable.

14 SUBMISSION OF TRIAL DATA

Participating research sites will be expected to maintain a file of essential trial documentation (Investigator Site File), which will be provided by the CTRU, and keep copies of all completed paper CRFs for the trial.

CTRU will provide electronic copies of trial-specific paper case report forms (CRFs) required for collection of informed consent and contact information. Participant completed questionnaires will be collected either on paper or electronically via patient reported outcome software dependent on participant choice.

Trial data collected on paper CRFs will be submitted to the CTRU usually via standard post or secure electronic transfer.

All other data collection will be via Remote Data Entry (RDE) on electronic case report forms (eCRFs) managed by the CTRU at the University of Leeds. Access to the live POLARiS database will be provided by the CTRU following sites authorisation to open to recruitment; An SSOP will offer guidance on RDE and completing eCRFs. Missing and discrepant data will be flagged, and additional data validations raised as appropriate from the CTRU data management team.

Data must only be completed by personnel authorised to do so by the PI, as recorded on the trial-specific Authorised Personnel Log.

Case Report Forms (CRFs), electronic CRFs (eCRFs), and participant-completed questionnaires will contain the participant's unique trial number, date of birth, and initials.

14.1 Death

Deaths that occur during the participant's 24 month follow up period must be reported to the CTRU using the Notification of Death eCRF on the POLARiS database **within 7 days** of site becoming aware of the event. Data collected with include (but not limited to):

- Date of death
- Cause of death

Receipt of a death form will stop the process of a notification of participant questionnaires to participants.

14.2 Definition of End of Trial

The end of the trial is defined as the date of the last participant's last data item.

14.3 Protocol Deviations

The CTRU undertake to adopt all reasonable measures to record data in accordance with the protocol. Under practical working conditions, however, some minor variations may occur due to circumstances beyond the control of the CTRU. All such deviations will be documented on the study records, together with the reason for their occurrence; where appropriate, deviations will be detailed in the published report.

15 SAFETY REPORTING

15.1 Cohort Safety Reporting

15.1.1 Cohort Definitions

'**Adverse Event' (AE)** – An Adverse Event in POLARiS Cohort is defined as an untoward medical event in a participant which is considered to be **related to the treatment of LARS**.

15.1.2 Reporting of AEs (Cohort)

Information about incidence and severity of adverse events considered to be **related** to the treatment of LARS, which occur from the date of registration until the end of the 24 month follow up period will be collected for cohort participants on the 12 and 24 month follow up eCRFs.

There are **no** expedited reporting requirements for the Cohort

15.2 RCT Safety Reporting

15.2.1 Trial Definitions

'**Adverse Event' (AE)** – An Adverse Event in POLARiS is defined as an untoward medical event in a participant which has a causal relationship with the trial or trial treatments.

'Serious Adverse Event' (SAE) – means an untoward occurrence that:

- results in death,
- is life-threatening,
- requires hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability,
- consists of a congenital anomaly or birth defect,
- is otherwise considered medically significant by the Investigator.

'**Related Unexpected Serious Adverse Event' (RUSAE)** – means for an SAE occurring to a research participant in the opinion of the Chief Investigator the event was:

- 'Related' that is, it resulted from the administration of any of the research procedures, and
- 'Unexpected' that is, the type of event is not listed in the protocol as an expected occurrence.

Medical and scientific judgement must be exercised in deciding whether an event is serious (see protocol section 15.3 for Responsibilities). These characteristics / consequences must be considered at the time of the event and do not refer to an event which hypothetically may have caused one of the above.

15.2.2 Expected Adverse Events

Examples of expected events within this trial are given below. This is not an exhaustive list.

Related to TAI

Adverse events relating to TAI are mainly practical problems with the irrigation procedure and include:

- pain with insertion of the catheter
- bleeding from the anus
- cramping abdominal pains
- expulsion of the catheter
- leakage of irrigation fluid beside the catheter
- dependency on caretaker help to perform irrigation
- Bowel perforation related to irrigation treatment is very rare with an incidence of less than 0.002% (18).

Related to SNM

Adverse events relating to SNM include:

- infection
- wound healing complications
- device failure or need for replacement batteries (batteries in more recent devices are often rechargeable and have a life span of 10-15 years).
- discomfort following stimulation
- undesirable changes in bowel or bladder function.

Related to OCM (medication)

Loperamide

- headaches
- dry mouth
- dry eyes
- Constipation

Amytriptyline

- drowsiness

15.2.3 Reporting of Adverse Events (RCT)

Information on all adverse events with a causal relationship to the trial or trial interventions will be collected for this trial whether volunteered by the participant, or detected by investigator on questioning, physical examination or other investigations.

Adverse events will be graded for severity using the CTCAE grading for all adverse events. Intra-operative adverse events will also be graded using the ClassIntra® classification of intraoperative adverse events, and post-operative adverse events will also be graded using the Clavien-Dindo Classification scale.

15.2.3.1 Serious Adverse Events (SAEs) and Related Unexpected Serious Adverse Events (RUSAEs) - Expedited Reporting

All Related Serious Adverse Events (SAEs) and Related Unexpected Serious Adverse Events (RUSAEs) occurring from a participant receiving their first trial procedure/treatment, until the end of the follow up are subject to expedited reporting requirements and must therefore be notified to the CTRU, via completion of the appropriate eCRF on the POLARiS Database, **within 24 hours** of the clinical research staff becoming aware of the event.

For each SAE and RUSAE, the following data will be collected:

- Start and end dates of event, if resolved
- Full details of event in medical terms with a diagnosis (if possible)
- Action/intervention
- Outcome
- An identifiable and authorised reporting source (i.e. electronic sign-off of the investigator or other medic authorised by the investigator at the reporting research site)

Any follow-up information on SAEs and RUSAEs must be entered onto the database as soon as it is available. Events will be followed up until resolution or a final outcome has been reached. All reportable SAEs and RUSAEs will be reviewed by the Chief Investigator (CI) or delegate and will be subject to expedited reporting to the Sponsor and the REC by the CTRU on behalf of the CI in accordance with current HRA guidance, CTRU Standard Operating Procedures (SOPs), and Sponsor requirements.

Expedited reporting requirements for Australian sites: Australian sites are **only required** to report **RUSAEs** in an expedited fashion. Related SAEs occurring in participants in Australia will be collected at the standard follow up time points and are not subject to expedited reporting to the CTRU.

15.2.3.2 All other Related AEs (non-serious) – Non-expedited reporting

Information about incidence and severity of all other **related** adverse events (this includes non-serious expected and unexpected related adverse events) which occur from the date of randomisation until the end of the 24 month follow up period will be collected for all participants on the operative and follow up eCRFs. These events will **not** be subject to expedited reporting requirements.

15.2.3.3 Untoward medical events unrelated to the trial – Not reportable

Untoward medical events classified as unrelated to the trial will not be collected.

15.3 Responsibilities For Safety Reporting

Principal Investigator (PI) (i.e. lead trial clinician at each recruiting research site or appropriate clinical individual identified in the APL)

- Checking for adverse events during admission and follow-up, including judgment in assigning:
  - Seriousness
  - Relatedness
  - Expectedness
- To ensure all SAEs (UK only) and RUSAEs are recorded and reported to the CTRU within 24 hours of becoming aware and to provide further follow-up information as soon as available.
- To report RUSAEs to local committees in line with local arrangements.

Chief Investigator (CI) (or nominated individual in CI's absence)

- Assign relatedness and expected nature of SAEs where it has not been possible to obtain local assessment.
- Undertake SAE review
- Review all events assessed as Related / Unexpected SAEs in the opinion of the local investigator. In the event of disagreement between local assessment and the CI, local assessment may be upgraded or downgraded by the CI prior to reporting to the REC.

Clinical Trials Research Unit (CTRU)

- Expedited reporting of Related / Unexpected SAEs to the REC and Sponsor within required timelines (UK only).
- Preparing annual safety reports to the REC and periodic safety reports to the Trial Steering Committee (TSC) and Data Monitoring & Ethics Committee (DMEC) as appropriate.
- Notifying Investigators of Related / Unexpected SAEs which compromise participant safety.

Expedited reporting of events (as detailed in section 15 to the REC and Sponsor will be subject to current HRA guidance, CTRU SOPs and Sponsor requirements.

Trial Steering Committee (TSC)

- Periodic review of safety data in accordance with the TSC Charter and CTRU policies, and liaising with the DMEC regarding safety issues.

Data Monitoring & Ethics Committee (DMEC)

- In accordance with the DMEC Charter and CTRU policies, periodic review of unblinded overall safety data to determine patterns and trends of events and to identify any safety issues which would not be apparent on an individual case basis.

16 ENDPOINTS

16.1 PRIMARY ENDPOINT

The primary endpoint is LARS score up to 24 months post-randomisation/registration*. The LARS score will be collected at baseline and 3-monthly until 24 months post-randomisation

16.2 SECONDARY ENDPOINTS

Secondary endpoints include:

- Health-related quality of life (EORTC QLQ-C29 and QLQ-C30) up to 24 months post-randomisation/registration*.
- Safety profile (nature and severity of adverse events – for definitions of adverse events on POLARiS see section 15) within 24 months post-randomisation/registration*
- Treatment compliance (RCT only) within 24 months post-randomisation
- Cost-effectiveness

*post-randomisation if the patient enters the RCT, post-registration to the cohort otherwise.

17 STATISTICAL CONSIDERATIONS

17.1 SAMPLE SIZE

For each of the two primary comparisons for the RCT - i) SNM vs OCM ii) TAI vs OCM – the sample size target to yield 85% power to detect the minimum clinically important difference (MCID) in LARS score at 24 months adjusted for baseline is 350 patients. It is estimated that 600 patients in total will need to be recruited to the RCT in order to hit these sample size targets. It is also estimated, under the same set of assumptions, that with the additional 200 Australian participants the total sample size will provide over 90% power to detect the MCID.

<u>MCID and sample size parameter assumptions</u>
According to NICE guidance, the MCID is defined as a 5 point difference in LARS [17].
Variability in LARS scores have been reported as standard deviation of around 11 points [2]. We have assuming, conservatively, a standard deviation of the 24-month LARS score of 15.

The primary outcome is LARS score at 24 months post-randomisation adjusted for baseline LARS score. The required sample size for the adjusted analysis can be obtained by multiplying the sample size requirement for the unadjusted analysis by a factor of (1-r^2), where r is the correlation between the 24-month and baseline LARS scores [30]. We have assumed that there will be at least a weak correlation between baseline and 24-month LARS scores of 0.3, and that sample size requirement for the unadjusted analysis can therefore be reduced by a factor of (1-0.3^2)=0.91.

It is also assumed that there will be no more than 15% attrition.

The number of patients recruited through three randomisation options: i) SNM vs TAI vs OCM ii) SNM vs OCM iii) TAI vs OCM and (see flowchart) are denoted n1, n2 and n3 respectively. It follows that (2/3)*n1 + n2 patients and (2/3)*n1 + n3 patients will contribute to the SNM vs OCM and TAI vs OCM comparisons respectively. It is assumed that 50% of RCT participants will be entered via randomisation option i), SNM vs TAI vs OCM, 25% via randomisation option ii) SNM only, and 25% via randomisation option iii) TAI only. It follows that for a total of N participants recruited to the trial, 0.25*N + (2/3)*0.5*N will contribute to each of the two primary comparisons.

Sample size requirement for a single comparison

326 participants would be sufficient to yield 85% power to detect the MCID in an (unadjusted) two-sided t-test of 24-month LARS scores at the 5% level of significance (nQuery v3.0).

Applying the factor of 0.91 due to adjusting for baseline LARS score, and the factor of 1/0.85 to account for attrition, we have a sample size target of 350 participants.

Therefore, recruiting a total of 600 participants results in 0.25*600 + (2/3)*0.5*600 = 350 patients contributing to each primary comparison, satisfying the sample size requirement.

18 STATISTICAL ANALYSIS

All analyses will be pre-specified in a Statistical Analysis Plan according to published guidance [31].

Analyses of the RCT will be conducted on an intention-to-treat basis, where all patients are analysed according to their randomised treatment, unless otherwise stated. Hypothesis tests will be 2-sided at the 5% level of significance. Point estimates of treatment effects will be reported with 2-sided 95% confidence intervals.

Comparative effectiveness analyses for each endpoint will consist of two pairwise treatment comparisons: TAI vs OCM and SNM vs OCM. Treatment groups will be combined across different randomisation options for gains in efficiency [32].

Let R1, R2 and R3 denote the randomisation options SNM:TAI:OCM, TAI:OCM and SNM:OCM respectively. The TAI vs OCM comparison will include patients from R2 and patients from R1 who were assigned to either TAI or OCM. SNM vs OCM comparison will include patients from R3 and patients from R1 who were assigned to either SNM or OCM.

Analysis of the cohort data will include exploratory model-fitting to evaluate the longitudinal trends in LARS scores in relation to patient characteristics and clinical data, as well as the identification of potential risk factors for major LARS.

Non-linearity of effects of continuous explanatory variables in all models will be considered, and explored and fitted as required via fractional polynomials or appropriate alternative (pre-specified in the Statistical Analysis Plan).

Further details in this section refer to the RCT analyses only.

18.1.1 PRIMARY ANALYSIS

The primary endpoint is LARS score up to 24 months post-randomisation/registration*. The LARS score will be collected at baseline and 3-monthly until 24 months post-randomisation, and will be analysed as a continuous variable.

For each of the pairwise comparisons (SNM vs OCM, and TAI vs OCM) the primary analysis plan is to estimate the expected difference in LARS scores at 24 months post-randomisation, using constrained longitudinal multi-level statistical model (cLDA) [33]. Transformations of the LARS score and/or non-Normal error assumptions will be considered as required based on the observed distribution of scores.

The stratification factors “Time between anterior resection and randomisation”, “Biological sex at birth” , “Age”, Radiotherapy and “Procedure” will be included as fixed effects in the model.

The model will account for nesting of repeated LARS score observations within patient, and the nesting of patients within “Centre” within “Country” by using appropriate variance components to model random effects [34] . Randomisation option will also be accounted for in the model [35]. The significance of the treatment effects will be derived from this statistical modelling approach reported with point estimates of treatment effects with 2-sided 95% confidence intervals.

Missing data mechanisms will be explored. Multiple Imputation using Chained Equations (MICE) will be considered to explore the potential impact of missing data under a MAR assumption, and to explore sensitivity of the results to MNAR mechanisms as required.

18.1.2 SECONDARY ANALYSES

For all continuous secondary endpoints - including the domain scores from the EORTC QLQ-C30, QLQ-CR29, two pairwise comparisons will be made (TAI:OCM, SNM:OCM), with analysis populations and modelling approaches as already described for the primary outcome measure. Transformations of the domain scores and/or non-Normal error assumptions will be considered as required based on the observed distribution of scores.

Questionnaire domains will be scored according to scoring manuals and reported graphically over time.

Adverse events will be reported descriptively.

19 ECONOMIC EVALUATION

This section describes the health economic evaluation for the UK. A separate Australian health economic evaluation will be performed as described in the Australian specific protocol.

The economic evaluation will compare the cost-effectiveness of Transanal irrigation (TAI) or Sacral neuromodulation (SNM) against optimised conservative management (OCM) for people with major LARS.

An early-stage model [36, 37] was developed alongside the protocol. This model was based on our experience in economic assessments of TAI and SNM devices to ensure that data collection plans meet the requirements of the economic analysis. Key drivers in previous models included frequency of use of TAI, carer costs, adverse events related to incontinence or constipation, adverse events related to SNM implantation and SNM device lifetime. This informed the health economic analysis plan (HEAP) that ensures appropriate data collection and pre-specified analysis [38].

Resource use will be collected as part of the clinical data collection and participant completed questionnaires at baseline, and at 3, 6, 12 and 24 months post-randomisation and will be combined with published unit costs. Resource use questionnaires completed by participants will be used to capture data such as primary, secondary and private health care resource use, out-of-pocket expenses on consumables, medicines, personal time and travel costs, whilst clinical CRFs will be used to capture initial and subsequent procedures, adverse events/complications, consumables, medicines and additional support/appointments.

The preferred method for NICE of measuring health-related quality of life in adults [39] is the EQ-5D. This will be collected using EQ-5D-5L from participants during the study and mapped to EQ-5D-3L utility values using a UK preference set through a crosswalk approach[40]. The quality-adjusted life years (QALYs) over 24 months will be estimated using the area under the curve method [41] . The study is also collecting EORTC QLQ-C30, which will be mapped to EQ-5D-3L to allow valuation as QALYs [42]. Costs and QALYs beyond 12 months will be discounted at the rate recommended by NICE.

The within-trial economic analysis over 24 months will be performed from the UK NHS and social services perspective. An appropriate regression model adjusted for minimization variables and baseline covariates will be undertaken to estimate the mean costs and outcomes between groups. Incremental cost-effectiveness ratios (ICERs) will be calculated, defined as incremental costs per additional QALY gained. Cost-effectiveness acceptability curves (CEAC) will be constructed using results from the non-parametric bootstrapping. Sensitivity and subgroup analyses including using a wider societal perspective and using utility values derived from EORTC QLQ-C30 will be undertaken if appropriate.

A decision analytic model will be constructed to extrapolate long-term costs and outcomes of the treatment groups. Trial data and literature will be used to populate the model. Deterministic and sensitivity analyses will be undertaken to characterize the uncertainty associated with the incremental costs and outcomes between treatment groups, and to determine the impact of key model inputs and assumptions on the findings. Results will be presented in ICERs and CEAC.

The reporting of this economic evaluation will comply with CHEERS recommendations [43].

20 TRIAL MONITORING

Trial supervision will be established according to the principles of GCP and in-line with the NHS UK Policy Framework for Health and Social Care. This will include establishment of a core Project Team, Trial Management Group (TMG), an independent TSC and independent DMEC. A Trial Monitoring Plan will be developed based on the trial risk assessment; this may include on site monitoring.

20.1 Trial Steering Committee (TSC) & Data Monitoring and Ethics Committee (DMEC)

An independent DMEC will be appointed to review the safety and ethics of the trial, alongside trial progress and the overall direction as overseen by the TSC. Detailed un-blinded reports will be prepared by the CTRU for the DMEC at approximately yearly intervals. The DMEC will be provided with detailed unblinded reports containing the information agreed in the data monitoring analysis plan. Trial progress will be closely monitored by the independent DMEC, who will report to the TSC, and the overall direction overseen by the TSC (ensuring regular reports to the NIHR Health Technology Assessment (HTA) Programme).

Following the 12 month internal pilot phase the DMEC and TSC will review trial progress to independently advise on progression of the trial to the funder. The trial will be reviewed against the pilot metrics detailed in section 16, alongside trial information/data collecting during the pilot phase, feedback from the qualtitative sub-study and the process evaluation, and any relevant external factors.

20.2 Data Monitoring

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until they are received, until confirmed as not available, or until the trial is at analysis. However missing data items will not be chased from participants (although missing questionnaires sometimes are).

The CTRU or Sponsor will reserve the right to intermittently conduct source data verification (SDV) exercises on a sample of participants, which will be carried out by staff from the CTRU or Sponsor. SDV will involve direct access to participant medical notes at the participating research sites and the ongoing central collection of copies of consent forms and other relevant investigation reports.

20.3 Clinical Governance Issues

To ensure responsibility and accountability for the overall quality of care received by participants during the trial period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the TSC and, where applicable, to individual research sites.

21 QUALITY ASSURANCE, ETHICAL CONSIDERATIONS, AND CONFIDENTIALITY

21.1 Quality Assurance

The trial will be conducted in accordance with the principles of GCP in clinical trials, NHS UK Policy Framework for Health and Social Care Research 2017 and through adherence to CTRU SOPs. The study may be subject to inspection and audit by Cardiff and Vale UHB R&D office under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research 2017.

21.2 SERIOUS BREACHES

The CTRU and Sponsor have systems in place to ensure that serious breaches of GCP or the trial protocol are picked up and reported. Investigators are required to **immediately** notify the CTRU of a serious breach (as defined in the latest version of the HRA SOP) that they become aware of. A 'serious breach' is defined as a breach of the protocol or of the conditions or principles of GCP (or equivalent standards for conduct of non-CTIMPs) which is likely to affect to a significant degree

a) the safety or physical or mental integrity of the trial subjects, or

b) the scientific value of the research

In the event of doubt or for further information, the Investigator should contact the Senior Trial Manager at the CTRU.

21.3 ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013. Informed written consent will be obtained from the participants prior to registration to the cohort and randomisation into the trial. The right of a patient to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment.

21.4 ETHICAL APPROVAL

Ethical approval in the UK will be sought through the Health Research Authority (HRA). The trial will be submitted to and approved by a REC, the HRA and the appropriate Site Specific Assessor for each participating UK research site prior to entering participants into the trial. The CTRU will provide the REC with a copy of the final protocol, participant information sheets, consent forms and all other relevant trial documentation.

22 INFORMATION GOVERNANCE AND CONFIDENTIALITY

Cardiff and Vale University Health Board and the University of Leeds are joint data controllers for the trial. Participating sites will be data processors for any trial data processing (while remaining data controllers of data processing required for patient care).

All data processing for the trial will be in accordance with the 2018 Data Protection Act. Personal data will be processed under a lawful basis of 'task in the public interest' (GDPR Article 6, 1(e)) and special categories of personal data (in this case, data about health, racial or ethnic origin and genetic data) will be processed for scientific research purposes (GDPR Article 9, 2(j)).

All trial participants (and any patients considered for the trial) are provided with detailed information about how their data will be processed before any trial data processing. Any material changes to how data will be processed will be communicated to trial participants in a timely manner (prior to the changes, if reasonably possible).

Personal data will only be processed for specified, explicit and legitimate purposes, and will be adequate, relevant and limited to those purposes. Data will be stored and transferred securely for all processing. The trial will undergo an information governance risk assessment at the CTRU to ensure its proposed processing is compliant with data protection laws.

Confidentiality of participant data will be maintained at all times, with access to data granted only to those who need it for legitimate reasons (i.e. to conduct the trial, or to ensure the trial has been conducted lawfully). Participants will allow access to their confidential data through the informed consent process. Copies of participant consent forms, which will include participants' names, will be collected when a participant is randomised into the trial by the CTRU. In addition, participant name and address may be collected for questionnaire posting or email address/phone number if the participant chooses to complete the questionnaires electronically. All other data collection forms that are transferred to or from the CTRU will be coded with a unique participant trial number and will include two participant identifiers, usually the participant's initials and date of birth. Data will be held securely on paper and electronically at the Clinical Trials Research Unit (CTRU) for the duration of the trial. The CTRU will have access to the entire database for monitoring, co-ordinating, and analysis purposes.

Sites are responsible for maintaining this pseudonymisation on any data sent to the CTRU. Any exceptions (e.g. collecting unredacted consent forms at the CTRU for central monitoring of informed consent) will only be for legitimate reasons and will be explained fully to participants in advance of data processing. Where central monitoring of source documents, or copies of source documents, is required by CTRU, the participant's name must be obliterated by site before sending. Any breach of confidentiality or of participants' personal data will be handled and reported (if required) in line with relevant laws.

Data will be made available for secondary research once the main trial objectives are complete.

If a participant withdraws consent from further trial treatment and/or further collection of data, their data will remain on file and will be included in the final trial analysis.

22.1 ARCHIVING

22.1.1 TRIAL DATA AND DOCUMENTS HELD BY CTRU

Trial data will be retained for a minimum of 5 years. When there is no longer a lawful basis for retaining the data, it will be securely destroyed. Trial data will be archived at an off-site external archiving service.

22.1.2 TRIAL DATA AND DOCUMENTS HELD BY RESEARCH SITES

Research sites are responsible for archiving all trial data and documents (ISF and all essential documents therein, including CRFs) at the participating research site until authorisation is issued from the Sponsor for confidential destruction.

22.1.3 PARTICIPANT MEDICAL RECORDS HELD BY RESEARCH SITES

Research sites are responsible for archiving trial participant medical records in accordance with the site's policy and procedures for archiving medical records of patients who have participated in a clinical trial. However, participant medical records must be retained until authorisation is received from the Sponsor for confidential destruction of trial documentation.

23 STATEMENT OF INDEMNITY

This is an NHS-sponsored research study, and the NHS indemnity scheme therefore applies in the UK. If there is negligent harm during the study when the NHS body owes a duty of care to the person harmed, NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. The NHS indemnity scheme does not cover non-negligent harm.

24 TRIAL ORGANISATIONAL STRUCTURE

Research sites will liaise with the CTRU for advice and support on trial set-up and operation, and submission of trial data. In turn, the CTRU will be responsible for data chasing.

24.1 OPERATIONAL STRUCTURE

Chief Investigator (CI): As defined by the NHS UK Policy Framework for Health and Social Care, the CI is responsible for the design, management and reporting of the trial.

UK Trial Sponsor-: Cardiff & Vale University Health Board are the sponsor within the UK only. The sponsor is responsible for trial initiation management and financing of the trial in the UK as defined by the Directive 2001/20/EC. The sponsor delegates some of these responsibilities to CTRU as detailed in the trial contract.

Clinical Trials Research Unit (CTRU): the CTRU at the University of Leeds will have responsibility for the conduct of the trial in accordance with the NHS UK Policy Framework for Health and Social Care and CTRU SOPs. The CTRU will provide set-up and monitoring of trial conduct to CTRU SOPs and the NHS UK Policy Framework for Health and Social Care including randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, ongoing management including training, monitoring reports and trial promotion, monitoring schedule and statistical analysis for the trial. In addition, the CTRU will support ethical approval submissions, any other site-specific approvals, and clinical set-up. The CTRU will be responsible for the overall day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting, and statistical analyses. At the end of the trial, CTRU will be responsible for archiving all data and trial data held by the CTRU in line with the Sponsor's procedures for a minimum of 5 years.

Centre for Healthcare Evaluation, Device Assessment and Research: CEDAR are responsible for the UK Economic Evaluation and the design, implementation, management and analysis of the qualitative sub-study and the process evaluation.

Research Sites (local PI): The responsibility for ensuring clinical management of participants is conducted in accordance with the trial protocol ultimately remains with the PI at each research site.

24.2 Management of the trial in Australia.

Up to 500 additional cohort participants and up to 200 additional RCT participants will be recruited from up to 15 hospitals in Australia.

Cardiff & Vale will act as Sponsor for the study in the UK only. The University of Sydney will be the sponsor in Australia and will provide no-fault clinical trial indemnity and insurance, execute clinical trial research agreements with participating hospitals and provide site payments. The NHMRC Clinical Trials Centre (CTC) at the University of Sydney will assume delegated sponsorship responsibilities and take responsibility for the study conduct in Australia. Responsibilities of the CTC will include (but are not limited to) submission of the study for all relevant regulatory approvals, submission of central ethics application, country-specific protocol (and all related documents) based on the approved UK documents, local site set-up including confirmation of local ethics and research governance approvals, local management of the trial and assessment of local safety reporting.

Australian participants will use the same registration/randomisation system as UK participants. Data from Australian participants will be entered directly onto the main trial specific databases developed by CTRU at the University of Leeds. CTRU will be responsible for managing and cleaning this data. Data presented to oversight committees will include data from UK and Australian participants. CTRU will be responsible for analysing the trial endpoints described in this protocol, data from both UK and Australian participants will be included in the final analysis.

The CTC's Health Economics Department will undertake an Australian health system cost effectiveness evaluation which includes healthcare resource utilisation & productivity losses, hospitalisation data and linked administrative data (Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Scheme (PBS) for consenting patients from Services Australia.

A collaboration agreement will be put in place between the UK sponsor, the University of Sydney and CTRU detailing local sponsorship, roles and responsibilities, safety reporting requirements and privacy requirements including the export of Australian data to the UK.

24.3 Oversight/Trial Monitoring Groups

Trial Management Group (TMG): the TMG, comprising the CI, CTRU team, CEDAR team, NHMRC CTC representatives and other key external members of staff involved in the trial, and patient representatives will be assigned responsibility for the clinical set-up, on-going management, promotion of the trial, and for the interpretation of results. Specifically the TMG will be responsible for:

- Protocol completion
- CRF development
- Obtaining approval from the HRA, UK REC and supporting applications for locally required approvals
- Completing cost estimates and project initiation
- Nominating members and facilitating the TSC and DMEC
- Reporting of adverse events
- Monitoring of screening, recruitment, treatment and follow-up procedures
- Auditing consent procedures, data collection, trial end-point validation and database development.

Trial Steering Committee (TSC): the TSC will provide overall supervision of the trial, in particular trial progress, adherence to protocol, participant safety and consideration of new information. It will include an Independent Chair, not less than two other independent members, and a consumer representative. The CI and other members of the TMG may attend the TSC meetings and present and report progress. The Committee will meet annually as a minimum and will consider recommendations made by the DMEC. Data provided to this committee will come from patients recruited both within the UK and Australia.

Data Monitoring and Ethics Committee (DMEC): the DMEC will include independent membership and will review the safety and ethics of the trial by reviewing interim data during recruitment and follow-up. The DMEC meeting will be conducted according to an agreed DMEC Charter and members will be provided with reports prepared by CTRU. The DMEC meeting will consist of open and closed sessions to discuss aggregate data and, in the closed session, data presented by randomised group. The Committee will meet annually as a minimum. Data provided to this committee will come from patients recruited both within the UK and Australia.

24.4 FUNDING

This project is funded by the National Institute for Health Research. National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (Grant Ref: NIHR134937) in the UK and NHMRC-NIHR Collaborative Research Grant in Australia (Ref: 2015501)

25 PUBLICATION POLICY

The trial will be registered with an authorised registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines, prior to the start of recruitment.

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributorship. Authorship decisions will be guided by standard requirements for authorship relating to submission of manuscripts to medical journals. These state that authorship credit should be based only on the following conditions being met (http://www.icmje.org):

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data
- Substantial contribution to drafting the article or revising it critically for important intellectual content
- Substantial contribution to final approval of the version to be published.

In light of this, the CI, other grant co-applicants, and relevant senior CTRU staff will be named as authors in any publication, subject to journal authorship restrictions. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial. POLARiS publications will be published on behalf of the 'POLARiS Group'. Key staff from the top 5 recruiting sites to the RCT will be included as members of the POLARiS Group subject to journal requirements.

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the analysis of the primary endpoint, either for trial publication or oral presentation purposes, without the permission of the TSC. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the trial until the first publication of the analysis of the primary endpoint.

On completion of the research project a draft final report will be submitted to the HTA programme (trial funder) by the CTRU, within 14 days. This will be peer reviewed and then published on the HTA website. The CTRU is obliged to provide NIHR/HTA with advanced notice of any publication relating to the trial; copies of any relevant materials intended for publication will be provided to NIHR/HTA according to the NIHR output policy.

26 QUALITATIVE SUB-STUDY – UK patients

Participants' own perceptions of how LARS and its treatments impact on symptom control and quality of life are the most important measure of treatment effect and cannot be measured with questionnaires alone [44]. Few qualitative studies have explored patient views on LARS treatments and care strategies [20]. The qualitative sub-study of the POLARiS trial aims to give participants a voice. In the UK it will be undertaken by qualitative researchers at CEDAR (Centre for Healthcare Evaluation, Device Assessment and Research), part of Cardiff & Vale UHB (an NHS organisation). A similar sub-study will be carried out in Australia by a suitably qualified researcher

26.1 RESEARCH QUESTION(S) FOR QUALITATIVE OUTCOMES

The purpose of the qualitative outcomes sub-study is to explore the impact of the trial interventions (TAI, SNM, OCM) on participants' i) quality of life; ii) activities of daily living; ii) LARS symptoms; iv) psychological functioning; as well as participants' views and experiences with the intervention to which they have been allocated and the wider support provided such as training/teaching, access to information, staff support and engagement.

26.2 RECRUITMENT

Participants who are randomised into the RCT from the UK will be given the opportunity to take part in up to 3 semi-structured interviews spread over the 24 months follow-up period of the study (Figure 1). The ICF for the RCT will include an optional item for potential participants to consent to being contacted by the Qualitative research team in CEDAR (C&V UHB) and for Leeds CTRU to share demographic data with CEDAR. With their agreement, consenting participants' contact information (already collected for the main trial) will be shared with the Qualitative research team, along with demographic information so that CEDAR staff are able to carry out purposive sampling of participants (see below).

The Qualitative research team will not have access to any identifiable data from participants who do not wish to take part in interviews. Refusal to participate in the interviews will in no way impact the participants' eligibility to take part in the other elements of the trial.

26.3 CONSENT

Participants who have expressed an interest in participating in interviews and have been included in the sample will be sent a PIS which specifically explains the interviews and an ICF for the interviews, by CEDAR, via their preferred method (post, email, or arranged by telephone). In the interview-specific PIS we ask participants to return an expression of interest slip to CEDAR with their contact information in a free post envelope or via email. Patients who give permission to be contacted about the study will be contacted by a researcher from CEDAR.

Participants will be given at least 24 hours to read the PIS and ask any questions before considering to take part. The interview is then arranged for a later date, either by phone or online via Teams, whichever is most convenient for the patient. The researcher will take consent immediately prior to the first interview. Participants can request a copy of the ICF to be sent to them. One reminder will be sent to participants who have expressed an interest but who have not returned their contact information.

26.4 SAMPLING

Longitudinal sampling (where a single participant is interviewed at 3 timepoints) with flexibility to also include participants at just a single timepoint will be used. This will maximise variability across interviewees and reduce the burden on individual patients while allowing researchers to capture changing views over time. Interview participants will be purposively sampled from sites across the UK to include participants of both sexes, of different ethnic or cultural backgrounds, a range of ages, and severity of symptoms. Participants will be over-sampled at baseline to account for withdrawals over time. We aim to recruit 48 patients for interview 1 (16 from each of 3 study arms), 36 at interview 2 (12 from each of 3 study arms), and 30 for interview 3 (10 from each of 3 study arms).

26.5 DATA COLLECTION

One-to-one, semi-structured interviews will be carried out at 3 timepoints throughout the trial as summarised in Table 11.

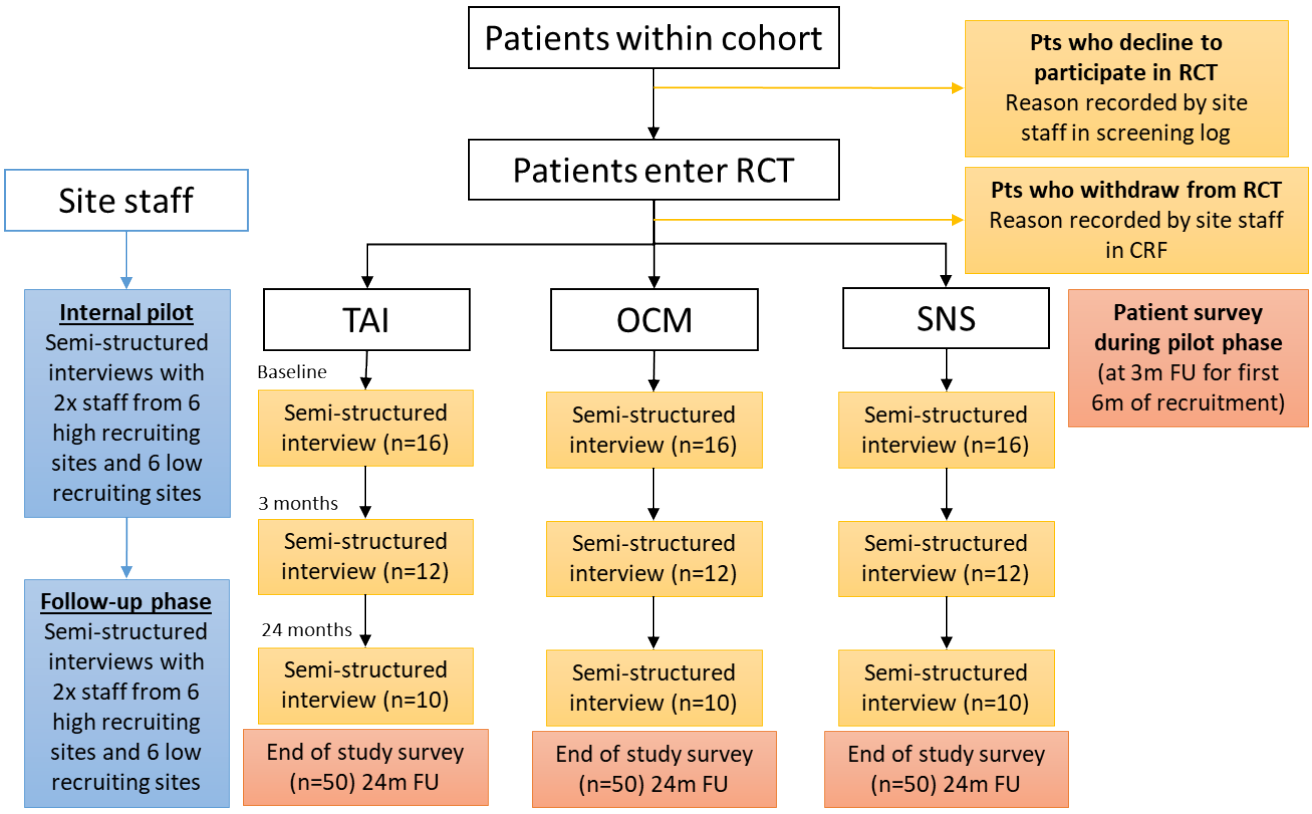
Table 11: Interview timepoints

Data source	Population and sample size	Timeframe
Interview 1	RCT participants (n= approx. 48; n=16 per arm x3)	Up to 6 weeks after randomisation (ideally prior to treatment starting).
Interview 2	RCT participants (n= approx. 36; n=12 per arm x3)	3 months (+/- 2 weeks) after commencing treatment
Interview 3	RCT participants (n= approx. 30; n=10 per arm x3)	At completion of follow-up (+/- 2 weeks)

Interview 1 will take place within 6 weeks of randomisation. Ideally this will be before treatment is commenced but in many cases this will not be possible, and in which case we will ask questions in relation to symptoms and treatment expectations prior to taking part in the trial. Interviews 2 and 3 will provide much more in-depth information about which aspects of the patient's day to day life has been impacted by the trial treatments. We do not anticipate interviews lasting longer than 60 minutes but there is no defined upper- or lower-time limit.

Interviews will be conducted by a trained qualitative researcher from CEDAR either over the phone or via Microsoft Teams or Zoom (following the wishes of the participant). Where possible, the same researcher will carry out longitudinal interviews with the same participant for consistency and continuity. An interview topic guide will be formulated with input from PPI representatives and healthcare professionals, and piloted before the start of data collection. Interviews will be recorded using either a password protected dictaphone (in the case of telephone interviews) or using the recording feature in Teams or Zoom. Audio files will be reviewed by a qualitative researcher and all potentially identifiable participant data will be removed prior to transcriptions. Anonymised recordings will be transcribed using an external company approved by the Sponsor (Cardiff & Vale UHB).

Figure 1: Schematic of qualitative sub-study and process evaluation data collection points



26.6 DATA ANALYSIS

Transcripts will be imported and coded using NVivo (QSR International). Analysis of the qualitative data will use a mainly iterative-inductive approach whereby emergent categories and ideas are generated based on specific observations and measures, rather than a priori concepts. This approach is committed to retaining diversity and complexity in the analysis. Furthermore, we aim to respect the uniqueness of individual cases as well as identifying comparative themes and patterns. Ritchie & Spencer's (1994) Framework Analysis [45, 46] will be used to facilitate the identification of patterns from reading transcripts. Further line by line coding will allow further identification of emerging themes, which will be refined as the analysis progresses. Results from this will

then be integrated with the results interpreted with reference to the results from the main trial to fully and accurately reflect their experiences of patients with LARS and the impact of the trial treatments.

27 PROCESS EVALUATION

The process evaluation of POLARiS will provide context to the efficacy findings of the study. It will use mixed methods to investigate the domains of acceptability, implementation; including fidelity, dose and reach, mechanisms of impact and context, as defined by MRC guidance [47] for process evaluations.

27.1 RESEARCH QUESTIONS

Research questions and their relation to process evaluation domains are outlined in Table 12.

Table 12: Research Questions

Process evaluation domain	Research questions (process evaluation)
Acceptability	1. Can there be improvements to the study procedures; including recruitment, training, interventions, assessments, communication, eligibility, randomisation and support? 2. What are the barriers and facilitators to recruitment and retention?
Implementation	3. What is the fidelity of the intervention for each arm of the study? 4. What is the proportion of interventions (planned TAI educational sessions, planned or additional OCM support) delivered to patients? 5. What is the rate of eligibility from cohort to RCT? 6. What is the conversion from RCT eligibility to randomisation? 7. What is the completion rate of participant questionnaires? 8. What is the adherence of participants to interventions?
Mechanisms of Impact	9. How do participants interact with the interventions?
Context	10. What are the contextual factors that explain why participants have a positive or negative experience of the study and its interventions? 11. How are the study interventions implemented, what are the contextual factors which explain this, and what factors explain differences in compliance?

Table 13 below describes the range of data collection sources, how they relate to the research questions, the timepoints, participants, recruitment arrangements, and analysis approach. Figure 1 provides a schematic of the approaches used for the PE.

27.2 RECRUITMENT, CONSENT, AND SAMPLING

Depending on the data source, participants or staff will be recruited and consented to contribute their data to the PE either through the usual consent process for the main trial, or a specific arrangement for interviews (these

are the same interviews as the qualitative sub-study described in section 26). See Table 13 for an overview of the recruitment approaches used for various data sources and see the Qualitative Sub-study section for details on how participants will be recruited to take part in the main interviews for the study.

27.3 Patient surveys

Patient surveys will be administered within the first 6 months of recruitment, in order to identify any problems or issues as early as possible, and at the end of the study to gather retrospective information relating to the running of the trial and implementation of treatments. Patient surveys administered during the pilot phase and end of the study are not mandatory. The surveys and will be administered via a website link which will be in the body of the email sent to patients within the 3-month and 24-month questionnaire follow-up packs for the main RCT which are sent to participants from Leeds CTRU. For those who receive the questionnaire packs as paper copies, there will be a link and QR code included on the cover letter. The survey will use MS forms and be hosted by CVUHB on CEDAR's website. Responses will be anonymous and no patient identifiable data will be collected.

27.4 Staff interviews

Staff interviews will be conducted within the first 6 months of recruitment to identify any problems or issues as early as possible, and within the last 6 months of recruitment to retrospectively gather information relating to the running of the trial to feed into the running of future trials. Sites will be contacted to invite their staff to participate in interviews, the PIS and ICF will be included in this invitation.. Staff can reply via email or an online expression of interest form to provide their contact details. This will be sent directly to a CEDAR member of staff who will contact them as soon as possible to answer any questions they may have. Consent will be taken over Teams at time of interview. Interviews will be carried out via Teams.

27.5 Mixed methods data collection for PE

Data sources used to inform the PE are from a variety of mixed methods, qualitative and quantitative approaches. These are outlined in Table 13 below.

27.6 Analysis & reporting

27.6.1 Qualitative analysis

Audio files from patient and staff interviews will be reviewed by a qualitative researcher and all potentially identifiable participant data will be removed prior to transcriptions. Anonymised recordings will be transcribed using an external company approved by the Sponsor (Cardiff & Vale UHB). Transcripts will be imported and coded using NVivo (QSR International). Free text responses from participant surveys will be imported into NVivo for analysis as required. Hybrid thematic analysis will be used to facilitate the categorisation of qualitative data into the process evaluation domains while allowing for iterative coding of unanticipated findings or topics beyond the scope of this study [48].

27.6.2 QUANTITATIVE ANALYSIS

Quantitative or ordinal data from participant surveys will be collated using SPSS. Descriptive methods will be used to analyse and display quantitative data.

27.6.3 INTEGRATION OF FINDINGS

Integration of the data will be achieved through: i) presenting example cases where themes and quotes are presented alongside participants' quantitative data; ii) data transformation where qualitative data will be coded and the codes counted for the whole sample, and then displayed alongside quantitative data; iii) joint displays of findings (graphs, tables, figures) from quantitative and qualitative data will be used to draw out new insights.

27.6.4 REPORTING

There will be a process evaluation pilot report to the TMG following the 12-month data collection point. This will facilitate the optimisation of study procedures for participants and staff. This pilot report will focus on acceptability and implementation. Discussion of the report will be facilitated at a planned feedback session with the TMG. The process evaluation will be on the TMG agenda throughout the study, with updates provided on any emerging issues.

At the conclusion of the study, the findings will be reported via academic publication, following the Standards for Reporting Qualitative Research (SRQR)[49]. Findings will also be reported at relevant national and international conferences and via the study team to their respective healthcare organisations. The TMG will work with relevant patient groups and charities at the conclusion of the study to translate the findings into appropriate patient facing materials to inform patients about the treatment options for LARS.

Table 13: Description of process evaluation (PE) methods

Data source	PE research question	Participants	Time point	Recruitment/consent	Details	Analysis
Mixed methods						
Online patient survey (pilot phase)	Acceptability; Implementation; Mechanism of impact; Context	All RCT participants for 6 months	At 3m follow-up, distributed to all participants for the first 6m of recruitment.	Main RCT recruitment and consent process. No separate consent process for PE.	An online survey will be administered using MS Forms with a combination of open and closed questions. A link will be sent to participants alongside their main trial questionnaires via Leeds CTRU. The survey will be hosted by CEDAR (Cardiff & Vale UHB). Reminders will be sent in line with main trial questionnaire schedule.	Descriptive & thematic
Online Survey (follow-up)	Acceptability; Implementation; Mechanism of impact; Context	RCT participants n=150 (50 from each arm)	At 24m follow-up, all patients until recruitment target is reached.	Main RCT recruitment and consent process. No separate consent process for PE.	An online survey will be administered using MS Forms with a combination of open and closed questions. A link will be sent to participants alongside their main trial questionnaires via Leeds CTRU. The survey will be hosted by CEDAR. Reminders will be sent in line with main trial questionnaire schedule.	Descriptive & thematic
Study records	Implementation; context.	RCT participants	Throughout study	Main RCT recruitment and consent process	Study records of screening, recruitment, intervention delivery, correspondence, notes from TMG meetings (all anonymised) will be shared with CEDAR.	Descriptive & thematic
Quantitative						
Case report forms	Implementation (data completion, fidelity of interventions, dose	RCT participants	Throughout study	Main RCT recruitment and consent process	Anonymised variables in CRF relevant to the PE will be sent to CEDAR researchers from Leeds CTRU.	Descriptive

	delivered, adherence to intervention).					
Qualitative						
Short survey – decline to participate in RCT	Acceptability; context	All cohort participants who decline RCT	At point of declining to participate	Main RCT screening process.	Site staff will record reason for declining to participate in screening log. CEDAR researchers will collate and identify key themes using anonymised data.	Thematic
Short survey – withdrawal from RCT	Acceptability; context	All participants who withdraw from RCT	At point of withdrawal	Main RCT processes.	Site staff will record reason for withdrawal in CRF. CEDAR researchers will collate and identify key themes using anonymised data.	Thematic
Staff interviews (pilot phase)	Acceptability; Implementation; Mechanism of impact; Context	12 site staff (surgeon & nurse from 6 high recruiting sites & 6 low)	6-12m into the study (pilot phase)	Recruitment process specific to site staff who volunteer to take part in interviews.	Site staff will be invited to volunteer for interviews using an online contact form on CEDAR website shared via Leeds CTRU and their local PI. PIS is sent via email. Consent taken prior to interview over video/telephone call. Semi-structured staff interviews by qualitative researcher at CEDAR. Approx 45 mins over MS Teams or Zoom.	Thematic
Staff interviews (follow-up phase)	Acceptability; Implementation; Mechanism of impact; Context	12-24 site staff (as above; longitudinal in some cases)	Last 6 months of the study.	Recruitment process specific to site staff who volunteer to take part in interviews.	As above	Thematic

Participant interviews (3 time points	Acceptability; Implementation; Mechanism of impact; Context	3 time points 16x3 arms=48; 12x3 arms=24; 10x3=30	Interview 1 - ideally before starting treatment; then 3 and 24m after treatment start	EoI during RCT to enable qualitative researchers to contact participants directly.	See qualitative sub-study section	Thematic

28 ABBREVIATIONS USED

ACRONYM	DEFINITION
AE	Adverse Event
API	Associate Principal Investigator
APL	Authorised Personnel Log
ASA	American Society of Anesthesiologists
CEAC	Cost-effectiveness Acceptability Curves
CEDAR	Centre for Healthcare Evaluation, Device Assessment and Research
CI	Chief Investigator
CRF	Case Report Form
CTC	Clinical Trials Centre
CTIMP	Clinical Trial of an Investigation Medicinal Product
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring and Ethics Committee
eCRF	electronic Case Report Form
EORTC	European Organisation for Research and Treatment of Cancer
FI	Faecal Incontinence
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HAR	High Anterior Resection
HEAP	Health Economics Analysis Plan
HRA	Health Research Authority
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental Cost-effectiveness Ratio
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
ISF	Investigator Site File
LARS	Low Anterior Resection Syndrome

MBS	Medicare Benefits Schedule
MCID	Minimum Clinically Importance Difference
MICE	Multiple Imputation using Chained Equations
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute of Health and Care Research
NHMRC	National Health and Medical Research Council
OCM	Optimised Conservative Management
PBS	Pharmaceutical Benefits Scheme
PE	Process Evaluation
PI	Principal Investigator
PIN	Personal Identification Number
PIS	Patient Information Sheet
PISICD	Patient Information Sheet and Informed Consent Document
PNE	Peripheral Nerve Evaluation
QALYs	Quality-adjusted Life Years
QoL	Quality of Life
RCT	Randomised Controlled Trial
RDE	Remote Data Entry
REC	Research Ethics Committee
RUSAE	Related Unexpected Serious Adverse Event
SAE	Serious Adverse Event
SDV	Source Data Verification
SLA	Service Level Agreement
SNM	Sacral Neuromodulation
SOP	Standard Operating Procedure
SRQR	Standards for Reporting Qualitative Research
SSOP	Site Standard Operating Procedure
TAI	Transanal irrigation
TMG	Trial Management Group

TSC	Trial Steering Committee
TWiC	Trial Within a Cohort
UK	United Kingdom
UHB	University Health Board
USC	Unexpected Serious Complication

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30 APPENDIX 1: CTCAE

Common Terminology Criteria For Adverse Events (CTCAE)

Events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events V5.0 (NCI-CTCAE).

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31 APPENDIX 2: Clavien-Dindo Classification of Complications

TABLE 1. Classification of Surgical Complications

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions
	Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications
	Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.
CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

32 Appendix 3: ClassIntra® v1.0 classification of intraoperative adverse events (iAE)

ClassIntra® v1.0 classification of intraoperative adverse events (iAE). The classification defines iAE as any deviation from the ideal intraoperative course occurring between skin incision and skin closure. Any surgery- and anaesthesia-related event during the index-surgery must be considered and should be rated directly after surgery.[1] A prerequisite is that the indication for surgery and the interventions conform to current guidelines. (BMJ, 2020, author Salome Dell-Kuster *et al.*)

Grade	Definition	Examples
Grade 0	No deviation from the ideal intraoperative course	
Grade I	Any deviation from the ideal intraoperative course • Without the need for any additional treatment or intervention • Patient asymptomatic or mild symptoms	• **Bleeding:** Bleeding above average from small-calibre vessel: self-limiting or definitively manageable without additional treatment than routine coagulation • **Injury:** Minimal serosal intestinal lesion, not requiring any additional treatment • **Cautery:** Small burn of the skin, no treatment necessary • **Arrhythmia:** arrhythmia (e.g. extrasystoles) without relevance
Grade II	Any deviation from the ideal intraoperative course • With the need for any additional minor treatment or intervention • Patient with moderate symptoms, not life-threatening and not leading to permanent disability	• **Bleeding:** Bleeding from medium calibre artery or vein, ligation; use of tranexamic acid • **Injury:** Non-transmural intestinal lesion requiring suture(s) • **Cautery:** Moderate burn requiring non-invasive wound care • **Arrhythmia:** Arrhythmia requiring administration of antiarrhythmic drug, no hemodynamic effect
Grade III	Any deviation from the ideal intraoperative course • With the need for any additional moderate treatment or intervention • Patient with severe symptoms, potentially life-threatening and/or potentially leading to permanent disability	• **Bleeding:** Bleeding from large calibre artery or vein with transient hemodynamic instability, ligation or suture; blood transfusion • **Injury:** Transmural intestinal lesion requiring segmental resection • **Cautery:** Severe burn requiring surgical debridement • **Arrhythmia:** Arrhythmia requiring administration of antiarrhythmic drug, transient hemodynamic effect
Grade IV	Any deviation from the ideal intraoperative course • With the need for any additional major and urgent treatment or intervention • Patient with life-threatening symptoms and/or leading to permanent disability	• **Bleeding:** Life-threatening bleeding with splenectomy; massive blood transfusion; ICU stay • **Injury:** Injury of central artery or vein requiring extended intestinal resection • **Cautery:** Life-threatening burn injury by cautery leading to fire requiring ICU treatment • **Arrhythmia:** Arrhythmia requiring electroconversion, defibrillation or admission to the ICU
Grade V	Any deviation from the ideal intraoperative course • With intraoperative death of the patient	

[1] The following events are not defined as intraoperative adverse events: sequelae, failures of cure, events related to the underlying disease, wrong-site or wrong-patient surgery or errors in indication