

# Ondansetron for Low Anterior Resection Syndrome after rectal cancer treatment

<b>Submission date</b> 25/02/2021	<b>Recruitment status</b> Stopped	<input type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 10/06/2021	<b>Overall study status</b> Stopped	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 09/05/2025	<b>Condition category</b> Digestive System	<input type="checkbox"/> Individual participant data <input type="checkbox"/> Record updated in last year

## Plain English summary of protocol

### Background and study aims

Rectal cancer is one of the most common cancers in the UK, and although chemo-radiotherapy and surgery are effective treatments, up to half of all patients report severe distressing problems after their treatment has finished. These include diarrhoea and problems with bowel control, ranging from needing to rush to the toilet (urgency), to complete bowel incontinence. This range of symptoms is known as "Low Anterior Resection Syndrome" (LARS) and can significantly affect quality of life. Unfortunately, at the moment, there are no effective treatments for LARS.

The symptoms of urgency and diarrhoea reported by LARS patients are similar to those in Irritable Bowel Syndrome (IBS). In IBS it has been shown that a cheap, widely available drug, called ondansetron. Ondansetron is normally used to treat nausea and vomiting and is effective and safe in treating diarrhoea and urgency.

The aim of this study is to find out if ondansetron helps resolve LARS symptoms.

### Who can participate?

Adult patients with LARS symptoms in from hospitals in England, at least 1 year after completion of all treatments for their rectal cancer

### What does the study involve?

To find out whether they are suitable to take part in the study, participants will first need to record details of symptoms and any medication taken for 2 weeks in a screening diary. Information in the screening diary will be reviewed by the research team who will confirm to the participant if they are eligible to take part.

Eligible participants will be allocated to one of two groups, with an equal chance of being in either group (like tossing a coin), so that half of the participants will receive ondansetron capsules and the other half will receive a placebo (this will look exactly the same as ondansetron but with no active ingredient). Neither the researchers nor the participants will know which capsules they are getting.

Participants will take ondansetron or placebo orally for 6 weeks, and complete a daily diary to record details on urgency, frequency, and consistency of their bowel movements, and any medications they have taken. Participants will also complete questionnaires about their bowel symptoms and quality of life, at the beginning and end of the trial.

What are the possible benefits and risks of participating?

Taking part in the study may not directly benefit participants, but information from the study will help to improve the treatment of people that suffer from the symptoms of LARS in the future.

Ondansetron has been widely used for over 25 years to treat nausea. As with all medications, there is a small risk of side effects. At the doses used in the study, the main side effect is expected to be constipation. Other common side effects include feeling hot and/or headaches. Uncommon side effects include arrhythmias (irregular heartbeat), chest pain, hiccups, low blood pressure, movement disorders, oculogyric crisis (upward rolling of the eyes), and seizure. Rare side effects include dizziness, QT interval prolongation (a problem with the heart's electrical activity), and vision disorders.

Where is the study run from?

Nottingham University Hospitals NHS Trust (UK). Participants will be recruited from at least 6 secondary care centres in the UK.

When is the study starting and how long is it expected to run for?

From July 2021 to April 2025

Who is funding the study?

The National Institute for Health Research (UK)

Who is the main contact?

researchsponsor@nuh.nhs.uk

## Contact information

**Type(s)**

Public

**Contact name**

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**Type(s)**

Scientific

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**Additional identifiers****EudraCT/CTIS number**

2020-004560-25

**IRAS number**

264493

**ClinicalTrials.gov number**

Nil known

**Secondary identifying numbers**

CPMS 44460, IRAS 264493

**Study information****Scientific Title**

Ondansetron for low Anterior Resection Syndrome (OARS) after rectal cancer treatment: a multicentre randomised blinded placebo-controlled parallel-group trial investigating the efficacy of ondansetron on symptoms

**Acronym**

OARS

**Study objectives**

The aim of this trial is to determine if ondansetron is tolerable and effective in reducing symptoms and improving quality of life in patients with low anterior resection syndrome (LARS).

**Ethics approval required**

Old ethics approval format

**Ethics approval(s)**

Approved 27/01/2021, North East - Newcastle & North Tyneside 2 Research Ethics Committee (NHS BT Blood Donor Centre, Holland Drive, Newcastle upon Tyne, Tyne and Wear, NE2 4NQ; +44 (0)207 1048091; newcastlenorthtyneside2.rec@hra.nhs.uk), ref: 21/NE/0015

## **Study design**

Multicentre blinded randomized placebo-controlled parallel-group trial

## **Primary study design**

Interventional

## **Secondary study design**

Randomised controlled trial

## **Study setting(s)**

Hospital

## **Study type(s)**

Treatment

## **Participant information sheet**

Not available in web format, please use the contact details to request a patient information sheet

## **Health condition(s) or problem(s) studied**

Low anterior resection syndrome following rectal cancer treatment

## **Interventions**

Eligible patients will be randomised (at a ratio of 1:1) to receive either ondansetron or matching placebo; the dose of ondansetron will be between 4-24 mg daily for 6 weeks. Dose titration will be undertaken in the first two weeks of the study to optimise the dose and avoid constipation. Treatment will be assigned using a secure, online computerised programme created and maintained by the Nottingham Clinical Trials Unit. Treatment will be assigned using a minimisation algorithm balancing on the following factors: recruiting site; LARS score at baseline (minor 21-29, major  $\geq 30$ ); and loperamide use over the 14 day baseline period (0 days, 1-6 days,  $\geq 7$  days).

The treatment period is 6 weeks and participants will be asked to complete a daily diary (online or paper option will be offered) which will collect important outcome data including stool frequency, consistency and urgency, and the number of study medication capsules taken. Participants will begin their study treatment by taking a single capsule of study medication per day.

Participants will be required to adjust the number of capsules of study medication they are taking every day from day 3 onwards, until they find the daily dose that best controls their symptoms. Participants will be given clear instructions on the process of titrating the dose of their study medication to control their symptoms and will be provided with contact information for their local site research team in case they have any questions or experience any problems. In addition, the research nurse or doctor will telephone the participant after 1 week and again after 2 weeks of taking the study medication to ensure that they are titrating the dose correctly and answer any questions/offer advice to the participant as required.

At the end of the 6 week treatment period participants will be sent study questionnaires to complete and return in the post.

## **Intervention Type**

Drug

## **Phase**

Phase II

## **Drug/device/biological/vaccine name(s)**

ondansetron

## **Primary outcome measure**

The proportion of days with no or mild urgency over the last 14 days of the planned 6 week treatment period measured using participant report in a daily diary between baseline and 6 weeks. Participants will record whether or not they had a bowel movement with urgency that day (yes or no), and those who responded yes will score their most urgent bowel movement that day as one of the following: mild (time able to delay bowel movement  $\geq 10$  mins), moderate (time able to delay bowel movement  $\geq 5$  to  $< 10$  mins), severe (time able to delay bowel movement  $\geq 1$  to  $< 5$  mins), or very severe (time able to delay bowel movement  $< 1$  min).

## **Secondary outcome measures**

1. Bowel dysfunction following a low anterior resection measured using the Low Anterior Resection Syndrome (LARS) questionnaire at 6 weeks
2. Bowel dysfunction score measured using the Memorial Sloan-Kettering Cancer Center (MSKCC) questionnaire at 6 weeks
3. Quality of life measured using the European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30) questionnaire and the EuroQol 5-dimension 5-level (EQ-5D-5L) questionnaire at 6 weeks
4. Psychological status measured using the Hospital Anxiety and Depression Scale (HADS) at 6 weeks
5. Anxiety measured using the anxiety subscale of the HADS at 6 weeks
6. Depression measured using the depression subscale of the HADS at 6 weeks
7. Percentage of participants with  $\geq 30\%$  improvement from baseline in the percentage of days with urgency for  $\geq 50\%$  of the days of the planned 6 week treatment period ("Urgency responders") measured using participant report of urgency in a daily diary between baseline and 6 weeks. Participants will record whether or not they had a bowel movement with urgency that day (yes or no), and those who responded yes will score their most urgent bowel movement that day as one of the following: mild (time able to delay bowel movement  $\geq 10$  mins), moderate (time able to delay bowel movement  $\geq 5$  to  $< 10$  mins), severe (time able to delay bowel movement  $\geq 1$  to  $< 5$  mins), or very severe (time able to delay bowel movement  $< 1$  min).
8. Percentage of participants with  $\geq 50\%$  improvement from baseline in the percentage of days with any stool consistency of 6 or 7 on the Bristol Stool Form Scale (BSFS) for more than 50% of the days of the planned 6 week treatment period ("Stool consistency responders") measured using participant report using the BSFS in a daily diary between baseline and 6 weeks.
9. Number of stools per day over the last 14 days of the planned 6 week treatment period measured using participant report of stool frequency in a daily diary between baseline and 6 weeks
10. Number of episodes of urgency per day over the last 14 days of the planned 6 week treatment period measured using participant report of urgency in a daily diary between baseline and 6 weeks

11. Proportion of participants taking study medication as required at the end of each week of the planned 6 week treatment period measured using participant report of the number of study medication capsules taken in a daily diary between baseline and 6 weeks and telephone conversation at 1 and 2 weeks
12. Proportion of days when study medication is taken during the planned 6 week treatment period measured using participant report of the number of study medication capsules taken in a daily diary between baseline and 6 weeks
13. The number of capsules of study medication taken daily during the planned 6 week treatment period measured using participant report of the number of study medication capsules taken in a daily diary between baseline and 6 weeks
14. Proportion of days when loperamide is taken during the planned 6 week treatment period measured using participant report of loperamide taken in a daily diary between baseline and 6 weeks
15. The dose of loperamide taken daily during the planned 6 week treatment period measured using participant report of loperamide taken in a daily diary between baseline and 6 weeks
16. Proportion of participants who report at the end of the 6 week treatment period that their LARS symptoms have improved from the start of the trial measured using the Low Anterior Resection Syndrome (LARS) questionnaire at baseline and 6 weeks
17. Frequency and severity of constipation experienced during the 6 week treatment period measured using participant report of constipation in a daily diary between baseline and 6 weeks
18. Frequency and type of new symptoms/health problems experienced during the 6 week treatment period measured using participant records at 6 weeks
19. Frequency of worsening of existing symptoms/health problems experienced during the 6 week treatment period measured using participant records at 6 weeks
20. Serious adverse events (including unplanned hospital admissions) during the 6 week treatment period measured using participant records at 6 weeks

**Overall study start date**

01/02/2020

**Completion date**

24/04/2025

**Reason abandoned (if study stopped)**

Participant recruitment issue

## Eligibility

**Key inclusion criteria**

1. Aged  $\geq 18$  years
2. Previously undergone standard total mesorectal excision (TME) resection with, or without, neoadjuvant chemoradiotherapy (CRT) for pT0-4, N0-2, M0 rectal cancer
3.  $\geq 1$  year after the end of any chemoradiotherapy and surgical treatment (ileostomy closure or primary resection if a stoma was not performed)
4. No evidence of rectal cancer recurrence
5. LARS questionnaire symptom score of  $\geq 21$  (minor or major LARS)
6. LARS symptoms to include both of the following:
  - 6.1. Presence of  $\geq 4$  bowel movements per day on average during the 14 days prior to the baseline visit
  - 6.2. Moderate, severe or very severe faecal urgency (unable to delay bowel movements by 10 min or more) on  $\geq 4$  days during the 14 days prior to the baseline visit

7. LARS symptoms not adequately controlled by current treatment
7. For participants of childbearing potential, or their partners, agreement to use medically accepted contraception (e.g. oral contraceptive and condom, Intra-uterine device (IUD) and condom, or diaphragm with spermicide and condom) for the duration of study treatment and for at least 30 days afterwards for women, and 90 days afterwards for men.
8. Able to read and understand questionnaires in English
9. Written informed consent provided

**Participant type(s)**

Patient

**Age group**

Adult

**Lower age limit**

18 Years

**Sex**

Both

**Target number of participants**

Planned Sample Size: 134; UK Sample Size: 134

**Total final enrolment**

0

**Key exclusion criteria**

1. Clinical and radiological anastomotic leakage after rectal cancer surgery, defined as a defect of the intestinal wall at the anastomotic site (including suture and staple lines of neorectal reservoirs) leading to a communication between the intra- and extraluminal compartments
2. Gastrectomy
3. Other known organic GI diseases (e.g. Crohn's disease, ulcerative colitis, coeliac disease)
4. Untreated thyroid dysfunction
5. Taking other medications influencing colonic motility (e.g. opioids, cholinergic agents, prokinetics, metoclopramide, cisapride, etc.) which are likely to be stopped or changed during the course of the trial
6. Lactose intolerance
7. Known QTc interval  $\geq 450$  ms for men and  $\geq 470$  ms for women
8. Continuous use of ondansetron for >1 month within the past year
9. Contraindications to ondansetron (e.g. concomitant use with apomorphine, hypersensitivity to any component of the preparation, rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption)
10. Currently participating in any interventional phase of another clinical trial
11. Pregnant or breastfeeding

**Date of first enrolment**

01/02/2020

**Date of final enrolment**

24/04/2025

# Locations

## Countries of recruitment

England

United Kingdom

## Study participating centre

**London North West University Healthcare NHS Trust**

Northwick Park Hospital

Watford Road

Harrow

United Kingdom

HA1 3UJ

## Study participating centre

**Salisbury NHS Foundation Trust**

Salisbury District Hospital

Odstock Road

Salisbury

United Kingdom

SP2 8BJ

## Study participating centre

**Shrewsbury And Telford Hospital NHS Trust**

Mytton Oak Road

Shrewsbury

United Kingdom

SY3 8XQ

## Study participating centre

**Hampshire Hospitals NHS Foundation Trust**

Aldermaston Road

Basingstoke

United Kingdom

RG24 9NA

## Study participating centre

**University Hospital Southampton NHS Foundation Trust**

Mailpoint 18

Southampton General Hospital

Tremona Road  
Southampton  
United Kingdom  
SO16 6YD

**Study participating centre**  
**Nottingham University Hospitals NHS Trust**  
Trust Headquarters  
Queens Medical Centre  
Derby Road  
Nottingham  
United Kingdom  
NG7 2UH

## **Sponsor information**

**Organisation**  
Nottingham University Hospitals NHS Trust

**Sponsor details**  
Research and Innovation  
Queen's Medical Centre  
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Nottingham  
England  
United Kingdom  
NG7 2UH  
+44 (0)115 9709049  
researchsponsor@nuh.nhs.uk

**Sponsor type**  
Hospital/treatment centre

**Website**  
<http://www.nuh.nhs.uk/>

**ROR**  
<https://ror.org/05y3qh794>

## **Funder(s)**

**Funder type**  
Government

**Funder Name**

National Institute for Health Research

**Alternative Name(s)**

National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

**Funding Body Type**

Government organisation

**Funding Body Subtype**

National government

**Location**

United Kingdom

## Results and Publications

**Publication and dissemination plan**

The dissemination of the proposed research findings will be via a NIHR report, research papers for publication in peer reviewed journals, presentation at medical conferences and communication to groups involved in guideline development. Results of this trial will be submitted for publication in a peer reviewed journal.

**Intention to publish date**

01/10/2026

**Individual participant data (IPD) sharing plan**

The datasets analysed during the current study will be available upon request from the NCTU (ctu@nottingham.ac.uk), a minimum of 6 months after publication of the main results paper. Access to the data will be subject to review of a data sharing and use request by a committee including the CI and sponsor, and will only be granted upon receipt of a data sharing and use agreement. Any data shared will be pseudoanonymised which may impact on the reproducibility of published analyses.

**IPD sharing plan summary**

Available on request

**Study outputs**

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">HRA research summary</a>			28/06/2023	No	No