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Ondansetron for Low Anterior Resection Syndrome after rectal cancer treatment

Submission date
25/02/2021

Recruitment status
Stopped

Registration date
10/06/2021

Overall study status
Stopped

Last Edited
09/05/2025

Condition category
Digestive System

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] 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

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Additional identifiers

Clinical Trials Information System (CTIS)
2020-004560-25

Integrated Research Application System (IRAS)
264493

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
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

Study type(s)
Treatment

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 ≥30); and loperamide use over the 14 day baseline period (0 days, 1-6 days, ≥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(s)
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 ≥10 mins), moderate (time able to delay bowel movement ≥5 to <10 mins), severe (time able to delay bowel movement ≥1 to <5 mins), or very severe (time able to delay bowel movement <1 min).

Key secondary outcome(s))
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 ≥30% improvement from baseline in the percentage of days with urgency for ≥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 ≥10 mins), moderate (time able to delay bowel movement ≥5 to <10 mins), severe (time able to delay bowel movement ≥1 to <5 mins), or very severe (time able to delay bowel movement <1 min).
8. Percentage of participants with ≥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

Completion date
24/04/2025

Reason abandoned (if study stopped)
Participant recruitment issue

Eligibility

Key inclusion criteria
1. Aged ≥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. ≥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 ≥21 (minor or major LARS)
6. LARS symptoms to include both of the following:
6.1. Presence of ≥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 ≥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

Healthy volunteers allowed

No

Age group
Adult

Lower age limit
18 years

Sex
All

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 ≥450 ms for men and ≥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
United Kingdom

England

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
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SY3 8XQ

Study participating centre
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RG24 9NA

Study participating centre
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SO16 6YD

Study participating centre
Nottingham University Hospitals NHS Trust
Trust Headquarters
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Derby Road

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NG7 2UH

Sponsor information

Organisation
Nottingham University Hospitals NHS Trust

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

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?
HRA research summary			28/06/2023	No	No