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Defining best management in adult chronic rhinosinusitis

Submission date	Recruitment status	[X] Prospectively registered
08/10/2018	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
17/10/2018	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
12/03/2026	Ear, Nose and Throat	

Plain English summary of protocol

Background and study aims
Chronic rhinosinusitis (CRS) is a long-term sinus disease affecting 1 in 10 adults in the UK. Symptoms of CRS include a blocked and runny nose, loss of smell, facial pain, tiredness, and worsening of breathing problems such as asthma. Studies have shown that sinus disease can have a greater impact on quality of life than heart disease and back pain. The type of treatments given by GPs and Ear, Nose and Throat specialists in the NHS varies greatly. This is due to doctors currently having limited information on how to effectively treat patients with CRS due to a lack of clinical trials in this area. Intranasal medications like nasal steroid sprays/drops and saline rinses (irrigations) play an important role in helping to improve CRS symptoms, and have been shown to be effective in trials. Saline rinses help wash away any excess mucus or irritants inside the nose, which can reduce swelling and relieve symptoms. Nasal steroid sprays/drops help to reduce inflammation. Nasal steroids and saline rinses are considered “standard care”. Other treatments given may include further medications to reduce swelling, such as antibiotics, or operations such as endoscopic sinus surgery (ESS), but there are few trials comparing these with standard care. The aim of this study is to establish which treatments work best for adults with CRS with and without nasal polyps (abnormal growths).

Who can participate?
Patients aged 18 and over with CRS

What does the study involve?
Throughout the 6-month duration of the trial all participants are asked to use standard care (intranasal medications), which are considered the current best practice for management of CRS. This intranasal medication includes nasal steroid drops/sprays and saline rinses. Participants are randomly allocated to receive one of the three treatment options: intranasal medication plus clarithromycin capsules, intranasal medication plus placebo (dummy) capsules or intranasal medication plus ESS. Participants take two capsules every day for the first two weeks, and then a normal dose of one capsule a day for the next 10 weeks (3 months in total). ESS is an operation on the sinuses performed through the nostril and guided by a small camera. The surgeon removes any polyps if present and then opens each sinus that is blocked to allow drainage.

Surgery is often performed as a day-case operation, but patients may need up to 10-14 days to recover fully from surgery. After 3 and 6 months the participants return to the outpatient clinic to see their doctor and/or research nurse and undergo assessments.

What are the possible benefits and risks of participating?
The researchers cannot guarantee that participating in this study will be of direct benefit. They hope to be able to improve the participants' CRS symptoms, but the main benefit will be the information that they gather, which will help to improve treatment options for patients with CRS in the future. Participants will be closely followed up by their ENT doctor and the MACRO Research Team whilst participating in the trial. The most common side effects of clarithromycin are: abdominal pain, diarrhoea, nausea, vomiting, change in sense of taste, headache, insomnia, dyspepsia, rash, hyperhidrosis, and abnormal liver function test. These side effects are usually mild. Complications of sinus surgery include: bleeding (affects 1 in 200), infection (affects 1 in 15), minor bleeding into the eye socket which is seen as bruising around eye (affects 1 in 500), more serious bleeding into the eye socket (very rare), direct trauma to the orbital contents may cause double vision or in extremely rare cases loss of sight (affects <1 in 10,000), leak of brain fluid and possible risk of meningitis if leak is not sealed (affects 1 in 1500), deep vein thrombosis (DVT) (less than 1% chance), clot on lung (pulmonary embolism) (0.3% chance), damage to teeth (1 in 5000), and reaction to anaesthetic drugs e.g. rash, high temperature (1 in 10,000, mild, 1 in 200,000 severe).

Where is the study run from?
1. James Paget Hospital (lead site)
2. Freeman Hospital
3. Guy's Hospital
4. Queen's Medical Centre
5. Royal Surrey County Hospital
6. Royal National Throat, Nose and Ear Hospital
7. Aintree University Hospital
8. Charing Cross Hospital
9. Derriford Hospital
10. Manchester Royal Infirmary
11. Ninewells Hospital
12. Norfolk and Norwich University Hospital
13. Queen Elizabeth Hospital
14. Royal Berkshire Hospital
15. Royal Infirmary of Edinburgh
16. University Hospital Lewisham
17. University Hospital Southampton

When is the study starting and how long is it expected to run for?
July 2017 to April2024

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
Stephen Jones
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Contact information

Type(s)
Scientific

Contact name
Mr Stephen Jones

Contact details
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Additional identifiers

Clinical Trials Information System (CTIS)
2018-001100-11

Integrated Research Application System (IRAS)
223922

Protocol serial number
38285

Study information

Scientific Title
Defining best Management in Adult Chronic RhinOsinusitis (MACRO): a randomised controlled trial

Acronym
MACRO

Study objectives
To establish the comparative effectiveness of a prolonged course of antibiotics (clarithromycin) or endoscopic sinus surgery (ESS) in adult patients with CRS in terms of symptomatic improvement and costs to the NHS and patients, compared with standard medical care (intranasal medication) and each other at 6 months.

Ethics approval required
Ethics approval required

Ethics approval(s)

Approved 11/07/2018, North East - Newcastle & North Tyneside 2 Research Ethics Committee (NHS BT Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, United Kingdom; -; newcastlenorthtyneside2.rec@hra.nhs.uk), ref: 18/NE/0210

North East – Newcastle and North Tyneside 2, 11/07/2018, ref: 18/NE/0210

Primary study design
Interventional

Study design
Randomised; Interventional; Design type: Treatment, Drug, Surgery

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Rhinosinusitis

Interventions
The MACRO Trial will investigate three different treatment options for patients with CRS. All participants who join the MACRO Trial will be asked to use standard care (intranasal medications), which are considered the current best practice for management of CRS. This intranasal medication includes nasal steroid drops/sprays and saline rinses.

The trial incorporates an internal pilot recruitment phase (first 6 months at 6 sites) with an embedded MACRO Conversation Study, before progressing to the full trial phase (a further ~11 sites).

INTERNAL RECRUITMENT PILOT PHASE (INCLUDING MACRO CONVERSATION STUDY)
The aim of the internal recruitment pilot phase is to randomise 72 participants at 6 pilot sites within 6 months. At least 3 sites should be open for the 6 month internal recruitment pilot phase to begin. Recruitment will be deemed successful if ≥75% of expected, i.e. 54 patients are recruited. A MACRO Conversation Study will be conducted as part of the pilot phase to identify any challenges to recruitment so that suggestions can be made to change aspects of design or conduct, recruitment strategies can be implemented and any training can be delivered to aid improvements in recruitment for the main trial phase. If recruitment is less than expected, we will propose a plan to increase recruitment based on the findings from the MACRO Conversation Study and communicate regularly with the funder.

MAIN TRIAL PHASE
On the basis of the pilot phase being successful, a further pre-identified 11 sites will be opened, and all 17 sites will recruit the remaining participants required to achieve a sample size of 600 within the funded timescale of the MACRO trial (estimated total trial duration is 52 months).

RECRUITMENT OF PATIENTS
The research nurse (RN) at each site will screen referral letters for adult patients with suspected CRS, coming from either primary care clinicians or secondary care colleagues. Where possible, these patients will be booked into MACRO outpatient research clinics to be seen by the PI or Co-

Investigator and RN. Screening logs should be completed by the RN and sent to the MACRO trial office on a monthly basis. The master screening log will remain at site and a copy of the screening log will be sent to the trials office.

RECRUITMENT OF PARTICIPANTS IN THE INTERNAL PILOT PHASE (MACRO CONVERSATION STUDY)
For potential trial participants seen during the internal recruitment pilot phase, a separate, MACRO Conversation Study Patient Information Sheet (PIS) will be presented to the patients by the RN for them to read whilst waiting in the outpatient department (prior to being seen in clinic). Any questions regarding the MACRO Conversation Study PIS can be answered by the RN prior to the patient entering the consultation with the PI/Co-I. Posters will also be placed in the outpatient department, with information relating to both the MACRO Conversation Study and MACRO trial. When consenting to the MACRO conversation study, participants will be consenting to the conversation element only and not to participate in the main clinical trial.

ALL PARTICIPANTS (BOTH IN INTERNAL AND MAIN TRIAL PHASE)
During the patient's routine clinic appointment, their doctor will discuss the MACRO Trial with them. The doctor will assess whether the patient is eligible to take part by looking at the results of their routine tests which include endoscopy, SNOT-22 questionnaire and CT scan. They will also explain that in order to receive treatment in the MACRO Trial, the patient will first need to undertake a trial-specific assessment in the form of an electrical heart tracing (ECG). This is to make sure that they can take clarithromycin safely. Women of childbearing age will also be asked to undertake a pregnancy test. If interested in the trial, the patient will be provided with a copy of the MACRO PIS to take home and review. The PIS will detail the exact nature of the study, what it will involve for the patient; the implications and constraints of the protocol and the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. In such an event, the choice of treatment will be a matter for decision between patient and their clinical team.

The RN should update the screening log and a MACRO sticker will be placed in the notes, to help identify the patient when returning to clinic. All patients will be allowed sufficient time (a minimum of 48 hours) to consider the trial and decide if they would like to take part. Screening logs must be kept up-to-date and fully completed at all times.

INFORMED CONSENT PROCEDURES

ICF FOR MACRO CONVERSATION STUDY DURING THE INTERNAL RECRUITMENT PILOT PHASE
During the internal recruitment pilot phase, potential participants will be asked if they have read the MACRO Conversation Study PIS in the waiting room prior to their clinic appointment and whether they would be happy to join this this element of the study. If in agreement, the patient will be provided with a separate MACRO Conversation Study Informed Consent Form (ICF) (this is different to the main trial consent, which is covered below) to sign immediately. Consent to join the MACRO Conversation Study immediately is requested because the aim of the MACRO Conversation Study is to record the consultations between the potential patient and the doctor as early as possible. If a patient requires more time to read the MACRO Conversation Study PIS (and therefore does not provide written ICF for the MACRO Conversation Study) they can instead give verbal consent to have the consultation recorded, and provide written consent at their next clinic appointment.

ICF FOR MAIN MACRO TRIAL
The potential participant will be telephoned by the RN at least 48 hours after being given the

MACRO PIS. The RN can answer any initial questions about the trial over the phone, and also invite the patient to return to clinic to discuss taking part in the MACRO trial in more depth.

The follow-up outpatient clinic appointment can either by conducted by the PI or Co-I, or the RN. As well as discussing details of the MACRO trial, the following elements of the consent process outlined:
1. A trial specific ECG must be carried out to confirm eligibility and consent is required for this
2. A pregnancy test must be undertaken by females of childbearing age and consent is required for this
3. The patient will be requested to consent to provide their e-mail address and mobile phone number to enable electronic completion of PROMs questionnaires and resource utilisation diaries. If the patient does not wish to consent to electronic completion of documentation (point 2), they will be asked instead to provide their home address and telephone number, so that the MACRO trial office can send the PROMs questionnaires and resource utilisation diaries by post
4. The participant has the option to consent to being contacted in the future about the MACRO Trial, or participating in other research studies participate in further related research
5. The participant has the option to consent to an interview with the Qualitative Researcher as part of the mixed methods evaluation
6. The participant has the option to consent to being followed-up annually for a period of 5 years, as part of the larger MACRO Programme of work. Participants participating in long-term follow-up will be requested to complete the SNOT-22 and EQ-5D-5L validated questionnaires, and a short diary on-line (a paper version is also available)

Once the participant's ECG result and pregnancy test (where relevant) has been reviewed and their doctor has confirmed they are eligible to enter the trial, they will then be allocated to their study treatment by a process called randomisation.

They will be randomly allocated to receive one of the three treatment options: intranasal medication plus clarithromycin capsules, intranasal medication plus placebo capsules or intranasal medication plus endoscopic sinus surgery. They will have an equal chance of getting one of these three treatment options.

BASELINE ASSESSMENTS
A comprehensive baseline assessment will be undertaken:
1. Clinical assessments:
1.1. Peak Expiratory Flow Measurement
1.2. Asthma control test (if known asthmatic)
1.3. Peak Nasal Inspiratory Flow Measurement
1.4. Sniffin' Sticks olfactory test
1.5. Skin prick allergy test (or RAST inhalant screen)
2. Blood tests to include full blood count and total IgE count
3. Eligibility confirmation
4. Participant demographics and medical history

Results of these assessments will be recorded on a baseline Case Report Form (CRF), along with data from the routine care pre-screening assessments:
1. Lund Mackay score from the CT scan
2. Lund-Kennedy score from the endoscopy
3. SNOT-22 score

Participants will be requested to complete the following baseline disease specific and generic PROMs questionnaires online: SNOT-22, SF-12 and EQ-5D-5L questionnaires during the baseline

visit. Participants will also be requested to complete online an initial baseline resource use questionnaire, which will ask participants about their use of health care services over the last 3 months before joining the trial. This questionnaire will be completed online by the participant, but during the baseline visit so that the research nurse is on hand to answer any questions. If any site has difficulties with doing these questionnaires online, a paper version is available.

EXPLANATION OF TREATMENT OPTIONS

INTRANASAL MEDICATION PLUS CLARITHROMYCIN CAPSULES AND INTRANASAL MEDICATION PLUS PLACEBO CAPSULES:
If the participant is allocated intranasal medication plus clarithromycin capsules OR intranasal medication plus placebo capsules, they will be told they have been allocated to the 'medical component' of the trial and will be asked to take capsules for 3 months. Because MACRO is a blinded trial, neither the participant, nor their doctor will know whether they are taking clarithromycin capsules or placebo capsules.

They will need to take an initial induction dose of two capsules every day for the first two weeks, and then a normal dose of one capsule a day for the next 10 weeks (3 months in total). The participant will also be asked to use nasal steroids sprays/drops and saline rinses throughout the 6-month duration of the trial. They will be given a Neil Med sinus rinse bottle and sachets for the saline rinses, and they should continue to use their prescribed nasal steroids sprays/drops. If they have not been prescribed any nasal steroids, their doctor will give them a prescription to take away with them.

INTRANASAL MEDICATION PLUS ENDOSCOPIC SINUS SURGERY:
If the participant is allocated intranasal medication plus endoscopic sinus surgery, they will be told they have been allocated to the 'surgical component' of the trial. They will be offered surgery within 6 weeks from the date that they joined the trial. Their doctor will go through what the surgery will involve (description below). They will also be asked to use nasal steroids sprays/drops and saline rinses throughout the 6-month duration of the trial, including both before and after the operation. They will be given a Neil Med sinus rinse bottle and sachets for the saline rinses, and they should continue to use their prescribed nasal steroids sprays/drops. If they have not been prescribed any nasal steroids, their doctor will give you a prescription to take away with them.

Endoscopic sinus surgery (ESS) is an operation on the sinuses performed through the nostril and guided by a small camera. The surgeon will remove any polyps if present and will then open each sinus that is blocked to allow drainage. The amount of surgery that is done will depend on the extent of swelling inside your nose and sinuses and this will determine the length of the operation. Surgery is often performed as a day-case operation, but patients may need up to 10-14 days to recover fully from surgery.

STUDY DURATION (ALL THREE ARMS)
The total study duration for the primary outcome data collection point is 6 months. After 3 and 6 months the participant will return to the outpatient clinic to see their doctor and/or research nurse and undergo the following assessments:
1. Nasal endoscopy
2. Peak Expiratory Flow Measurement
3. Asthma control test (if known asthmatic)
4. Peak Nasal Inspiratory Flow Measurement
5. Sniffin' Sticks olfactory test

They will separately be asked to complete a number of resource use and quality of life questionnaires. These are vital aspects of the trial, as they record how the participant is feeling, if their symptoms are getting better, how much medication they are using and how many times they have been to see a doctor. Their doctor or research nurse will go through these with the participant, and they will be asked to complete them on-line (a paper version is also available). The participant will be sent e-mails and text reminders to complete these, or reminders in the post if they have chosen to complete paper versions. A member of the central MACRO Trial Office may contact the participant by telephone from time to time if they have not completed these documents and to see if they require any assistance. Those participants who have consented to being contacted once a year, for a total of 5 years, will be contacted by the MACRO Research Team will contact the participant once a year and ask them to complete some short questionnaires online (paper version also available).

Intervention Type
Mixed

Primary outcome(s)
Disease-specific health related quality of life (HRQoL) measured using the SNOT-22 patient reported outcome measure (PROM) questionnaire at 6 months

Key secondary outcome(s)
1. Endoscopic score (Lund-Kennedy Score)
2. Grade of polyps (0 – 3, Lildholdt Score)
3. Health-related quality of life and quality-adjusted life-years (QALYs), measured using the SF-12v2 and EQ-5D-5L PROM questionnaires
4. Need for further treatment (e.g. oral steroids, antibiotics etc)
5. Olfactory function measured using Sniffin' Sticks
6. Upper and lower respiratory function, measured using peak expiratory flow rate, peak nasal inspiratory flow rate
7. Asthma Control Test (participants with asthma only)
8. Adverse events of treatment
9. Healthcare resource use, including medications and visits to primary and secondary care, recorded using patient diaries
10. Days of work missed, recorded using patient diaries
11. Overall cost and incremental cost per quality-adjusted life-year gained, from the cost perspective of the NHS and PSS, calculated using quality of life scores
12. Budget impact of treatment

Completion date
30/04/2024

Eligibility

Key inclusion criteria
Current inclusion criteria as of 13/09/2022:
1. Adults aged 18 and over with a diagnosis of CRS according to European guidelines:
A minimum of 12 weeks history of inflammation of the nose and paranasal sinuses characterised by two or more symptoms, one of which should be either nasal blockage/obstruction/ congestion or nasal discharge (anterior/posterior nasal drip):
± facial pain/pressure
± reduction or loss of smell

2. Nasal endoscopy (within last 3 months) to determine CRS diagnosis and phenotype (CRSwNPs or CRSsNPs)
3. Non-contrast CT scan (within last 18 months) to determine Lund-Mackay score and confirm suitability for ESS
4. Moderate/severe symptoms; SNOT-22 score ≥ 20 (within last 3 months)
5. Symptom control not achieved following previous Appropriate Medical Therapy (AMT), as deemed by the local Principal Investigator (PI) or Co-Investigator (Co-I), and therefore considered eligible for ESS
6. An understanding of the English language sufficient to understand written and verbal information about the trial, its consent process and the study questionnaires

Previous inclusion criteria:
1. Adults aged 18 and over with a diagnosis of CRS according to European guidelines:
1.1. A minimum of 12 weeks history of inflammation of the nose and paranasal sinuses characterised by two or more symptoms, one of which should be either nasal blockage /obstruction/ congestion or nasal discharge (anterior/posterior nasal drip):
1.1.1. ± Facial pain/pressure
1.1.2. ± Reduction or loss of smell
2. Nasal endoscopy (within last 3 months) to determine CRS diagnosis and phenotype (CRSwNPs or CRSsNPs)
3. Non-contrast CT scan (within last 12 months) to determine Lund-Mackay score and confirm suitability for ESS
4. Moderate/severe symptoms; SNOT-22 score ≥ 20 within last 3 months
5. Symptom control not achieved following previous AMT, as deemed by the local Principal Investigator (PI) or Co-Investigator (Co-I), and therefore considered eligible for ESS
6. An understanding of the English language sufficient to understand written and verbal information about the trial, its consent process and the study questionnaires

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
120 Years

Sex
All

Total final enrolment
514

Key exclusion criteria

Current exclusion criteria as of 13/09/2022:
1. Lund-Mackay non-contrast CT scan score <4
2. Macrolide antibiotic treatment for >3 continuous weeks' duration within the last 12 months
3. ESS in the previous 6 months or visible fronto-ethmoidal, open sinus cavities (including Draf III /modified Lothrop) from previous surgery
4. Oral/IV/Depot steroids within one month of baseline visit
5. Active treatment with biologic therapies which may modulate disease severity in CRS
6. Rare/complex sinus conditions:
6.1. CRS secondary to systemic disease - cystic fibrosis, granulomatous diseases
6.2. Suspected malignancy
7. Allergic fungal rhinosinusitis confirmed or suspected on CT imaging (expansion and mixed density opacification) necessitating immediate surgery
8. Severe asthma (high doses of inhaled steroids i.e. >1.5 mg per day)
9. Females who are pregnant or breastfeeding, females of reproductive potential not prepared to use a reliable means of contraception (e.g. hormonal contraceptive patch, intrauterine device, physical barrier or abstinence, if preferred and usual lifestyle of the patient) at trial entry or those females wanting to start a family during the initial 3 months of the trial
10. Known immunodeficiency states including HIV and selective and multiple antibody deficiency states
11. Severe septal deviation preventing endoscopic examination
12. Contraindications to surgery (significant medical co-morbidity)
13. Any absolute contraindications to clarithromycin (risk factors to be assessed at screening include a history of ischaemic heart disease, prolonged Q-T interval on ECG, or any medications known to interact with clarithromycin unless these can be discontinued during the 3 months of clarithromycin/placebo treatment, see appendix 5)
14. Known allergies to the IMP and excipients of IMP and placebo
15. Inability to give consent (significant cognitive impairment or language issues) or to understand and comply with trial instructions
16. Participation in another Randomized Clinical Trial in the past 4 months

Previous exclusion criteria:
1. Lund-Mackay non-contrast CT scan score <4
2. Macrolide antibiotic treatment for >3 continuous weeks' duration within the last 12 months
3. ESS in the previous 6 months or visible, open sinus cavities from previous surgery
4. Maintenance oral steroids or biologics
5. Rare/complex sinus conditions:
5.1. CRS secondary to systemic disease - cystic fibrosis, granulomatous diseases
5.2. Suspected malignancy
6. Allergic fungal rhinosinusitis confirmed or suspected on CT imaging (expansion and mixed density opacification) necessitating immediate surgery
7. Severe asthma (high doses of inhaled steroids i.e. > 1.5mg per day)
8. Females who are pregnant or breastfeeding, females of reproductive potential not prepared to use a reliable means of contraception (e.g. hormonal contraceptive patch, intrauterine device, physical barrier or abstinence, if preferred and usual lifestyle of the patient) at trial entry or those females wanting to start a family during the initial 3 months of the trial
9. Known immunodeficiency states including HIV and selective and multiple antibody deficiency states
10. Severe septal deviation preventing endoscopic examination
11. Contraindications to surgery (significant medical co-morbidity)
12. Any absolute contraindications to clarithromycin (risk factors to be assessed at screening include a history of ischaemic heart disease, prolonged Q-T interval on ECG, diabetes and age over 65 or any medications known to interact with clarithromycin unless these can be

discontinued during the 3 months of clarithromycin/placebo treatment)
13. Known allergies to the IMP and excipients of IMP and placebo
14 Inability to give consent (significant cognitive impairment or language issues), or to understand and comply with trial instructions
15. Participation in another Randomized Clinical Trial in the past 4 months

Date of first enrolment
01/11/2018

Date of final enrolment
13/10/2023

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
James Paget Hospital (lead site)
Lowestoft Road
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NR31 6LA

Study participating centre
Freeman Hospital
Freeman Road
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Study participating centre
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Study participating centre
Queen's Medical Centre
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Study participating centre
Royal Surrey County Hospital
Egerton Road
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Study participating centre
Royal National Throat, Nose and Ear Hospital
330 Gray's Inn Road
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Study participating centre
Aintree University Hospital
Longmoor Lane
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L9 7AL

Study participating centre
Charing Cross Hospital
Fulham Palace Road
London
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W6 8RF

Study participating centre
Derriford Hospital
Derriford Road
Crownhill
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PL6 8DH

Study participating centre
Manchester Royal Infirmary
Oxford Road
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Ninewells Hospital
James Arrott Drive
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Colney Lane
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Royal Berkshire Hospital
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Sponsor information

Organisation
University College London

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Government

Funder Name
NIHR Central Commissioning Facility (CCF); Grant Codes: RP-PG-0614-20011

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Stored in publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		30/08/2025	01/09/2025	Yes	No
Results article	Qualitative study	11/03/2026	12/03/2026	Yes	No
Protocol article		29/04/2019	09/11/2022	Yes	No
HRA research summary			28/06/2023	No	No
Other publications	maximising recruitment methods	13/01/2021	14/01/2021	Yes	No
Participant information sheet	version V3.0	31/08/2018	02/04/2019	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes