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The MOOSE study: a trial to compare whether methotrexate injections are better at controlling rheumatoid arthritis, have less side effects and are more cost-effective than oral methotrexate tablets

Submission date
24/03/2023

Recruitment status
No longer recruiting

Registration date
03/08/2023

Overall study status
Ongoing

Last Edited
18/11/2025

Condition category
Musculoskeletal Diseases

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Rheumatoid arthritis (RA) is treated with medicines such as methotrexate (MTX) that control inflammation and prevent joint damage. MTX is usually prescribed as weekly tablets for treating RA. If side effects are experienced, participants may be prescribed weekly injections of MTX instead of tablets.
A small amount of evidence suggests that MTX injections are more effective in controlling arthritis and cause fewer side effects than tablets. However, injections cost 20 times more than MTX tablets. This study will find out whether MTX injections are more effective than tablets in controlling RA, improving wellbeing, and whether MTX injections are acceptable to people with arthritis and value for money for the NHS.

Who can participate?
Adults who have not previously been prescribed MTX for their RA treatment

What does the study involve?
MOOSE will be conducted in rheumatology centres in 30 hospitals. Whether participants are prescribed MTX as a tablet or as an injection will be decided randomly. A research nurse will see participants at the start of the study. RA will be assessed by examining the joints and taking a blood sample to measure the level of inflammation. MTX treatment will start at a low dose and may be increased at the clinic visits over the next 2-3 months, depending on how the participant' s RA is improving and if they are having side effects. At 12, 24 and 52 weeks, one of the clinical care team will carry out the RA assessment. They will not know which treatment the participant has been taking so their assessment cannot be influenced by this.

Participants will complete questionnaires before their clinical assessment, with the help of the research nurse. They will ask about their arthritis, daily activities and work, well-being, fatigue,

and mental health. Also, 20 participants will be invited to take part in treatment acceptability interviews, at 1-2 months and 6-8 months. Participation is for 12 months or until the final clinical assessment.

What are the possible benefits and risks of participating?
Methotrexate is a long-standing treatment for rheumatoid arthritis and as such participants will have no greater risk than standard care. If participants experience side effects in either arm of the trial, these will be assessed as part of their usual clinic visits and the clinician will manage their treatment accordingly, as per standard care. Outside of clinical visits, a helpline phone number will be made available. Questionnaires will be given to patients at six timepoints, covering five different topics such as 'about your arthritis'. Some of the questions included may be sensitive and could lead to some distress to the patient, however, the likelihood of this occurring is low and comparable to sharing information at a standard care appointment. At baseline, 3 months, 6 months, and 12 months, questionnaires will be completed at clinic appointments, with the help of a research nurse if necessary, so patients will have the opportunity to discuss their current experience of their RA with their local care team. At 1 month and 2 months, questionnaires will be completed at home, and we will remind participants that they can contact their local care team using contact details provided on the PIS if they have any uncertainties.
When participants are taking part in the qualitative study, the interviewer will ask questions similar to the information they would share with a healthcare professional during an RA visit. The researcher would advise the patient to share any information that could impact their care with their local team after the interview.
Due to the risk of malformations associated with methotrexate, patients of childbearing potential will be asked to take a pregnancy test during the baseline visit, and in the absence of pregnancy, effective contraception must be used for the duration of the trial and 6 months thereafter. This will be discussed as part of the methotrexate educational training. The PIS clearly states that participants must not become pregnant whilst taking methotrexate or for 6 months after they stop taking methotrexate.

Where is the study run from?
City Hospital Nottingham (UK)

When is the study starting and how long is it expected to run for?
March 2023 to January 2027

Who is funding the study?
National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme (UK)

Who is the main contact?
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Additional identifiers

Integrated Research Application System (IRAS)
1006576

Protocol serial number
23006

National Institute for Health and Care Research (NIHR)
1006576

Central Portfolio Management System (CPMS)
56059

Study information

Scientific Title
Multi-centre randomised open-label assessor-blinded two-arm parallel-group trial of subcutaneous versus oral methotrexate for rheumatoid arthritis with internal feasibility assessment, economic evaluation and qualitative study

Acronym
MOOSE

Study objectives

1. To assess the effectiveness of a treat-to-target protocol using first-line subcutaneous methotrexate on remission assessed at 24 weeks
2. To assess the effectiveness of a treat-to-target protocol using first-line subcutaneous methotrexate on:
2.1. Disease activity
2.2 Quality of life
2.3 Mental health
2.4. Employment
2.5. Cost-effectiveness
2.6. Progression to other disease-modifying anti-rheumatic drugs including biologics
2.7. To assess the acceptability of first-line subcutaneous and oral methotrexate in a treat-to-target protocol

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 02/08/2023, South Central - Berkshire Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8233; berkshire.rec@hra.nhs.uk), ref: 23/SC/0125

Primary study design
Interventional

Allocation
Randomized controlled trial

Masking
Blinded (masking used)

Control
Active

Assignment
Parallel

Purpose
Prevention, Treatment

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Rheumatoid arthritis

Interventions
The MOOSE trial aims to compare the clinical and cost-effectiveness of subcutaneous and oral methotrexate in adults with rheumatoid arthritis (RA) and to collect information about the acceptability of both routes of methotrexate administration.

Intervention
The intervention is methotrexate, administered by subcutaneous injection. Starting dose will be in the range of 7.5 to 15 mg/week, with 4-weekly dose escalation, not to exceed 25 mg/week. A higher or lower starting dose will be permitted if this was the usual practice of the patient's rheumatologist.

Comparator
The comparator is oral methotrexate, administered in tablet form. Starting dose will be in the range of 7.5 to 15 mg/week, with 4-weekly dose escalation, not to exceed 25 mg/week. A two- or three-weekly dose escalation will be permitted if this was the usual practice of the patient's rheumatologist.

Randomisation
Patients with newly diagnosed RA, who have not previously been treated with methotrexate, have consented to take part in MOOSE, and meet the eligibility criteria, will be randomised to either subcutaneous or oral methotrexate. Treatment will be assigned randomly using a minimisation algorithm balancing by trial recruiting centre, DAS-28-CRP (<5.1 and ≥5.1) and disease duration (<4 months, 4-12 months, and >12 months). Allocation will be concealed using a web-based randomisation system developed and maintained by the Nottingham Clinical Trials Unit (NCTU).

Follow-up
The treatment period is 52 weeks from randomisation to the end of follow-up. Allocated treatment for both arms may be stopped or changed at any point during the follow-up period, on the guidance of the participant's rheumatologist. In both arms of the trial, participants will have the same follow-up schedule.

Screening visit
During their first routine RA clinic visit, eligible patients will be approached to see if they would like to take part in the MOOSE trial.

Baseline visit
On the patient's next clinic visit, if they are willing to initiate methotrexate treatment and take part in MOOSE, eligibility will be assessed and informed consent taken. Clinical RA assessments will be completed prior to randomising the patient. After randomisation, baseline questionnaires will include global assessment, participant pain, Health Assessment Questionnaire Disability Index (HAQ-DI), 5 level EuroQol 5 dimensional (EQ-5D-5L), RA-QoL, Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F), Patient Health Questionnaire Depression Scale (PHQ-8), Generalised Anxiety Disorder Assessment (GAD-7), and Work Productivity and Activity Impairment questionnaire – Rheumatoid Arthritis (WPAI-RA).

Dose escalation visits
Dose escalation will occur at weeks 4 and weeks 8 as part of routine clinic visits. At weeks 4 and 8 during the dose escalation period, participants will complete the global assessment, participant pain, infections and side effects, Theoretical Framework of Acceptability Questionnaire (TFAQ), and Beliefs about Medicine Questionnaire (BMQ), at home via an online questionnaire.

Study assessment visits
Study assessment visits will occur at weeks 12, 24 and 52. At each of these visits, clinical assessments will be used to calculate a DAS-28-CRP score. At each follow-up visit participants will also complete outcome questionnaires to include the global assessment, participant pain,

infections and side effects, HAQ-DI, EQ-5D-5L, RA-QoL, FACIT-F, PHQ-8, GAD-7, WPAI-RA, TFAQ, and BMQ.

Participant interviews
Participants will have the option to take part in treatment acceptability interviews at weeks 4-8 and 24-32.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Methotrexate injections, methotrexate oral tablets

Primary outcome(s)
Remission of rheumatoid arthritis (RA), defined as DAS-28-CRP <2.6, at 24 weeks

Key secondary outcome(s))
The following endpoint evaluations will coincide with clinic visits and questionnaires completed at 4, 8 12, 24 and 52 weeks after commencing the trial and starting methotrexate treatment:
1. Remission of rheumatoid arthritis (RA) at 12 and 52 weeks, defined as DAS-28-CRP <2.6
2. Remission of RA at 12, 24 and 52 weeks, as per 2022 Boolean American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) definition, Simplified Disease Activity Index
3. Disease activity at 12, 24 and 52 weeks, defined as DAS-28-CRP, Clinical Disease Activity Index, Simplified Disease Activity Index and components of these scores
4. Response to treatment at 12, 24 and 52 weeks, defined as DAS-28-CRP; EULAR and ACR 20, 50, 70 responses
5. Function measured using HAQ-DI at 12, 24 and 52 weeks
6. Quality of life, fatigue, anxiety, and depression measured using RA-QoL, FACIT-F, GAD-7, PHQ-8, and EQ-5D-5L at weeks 24 and 52
7. Work productivity and employment measured using WPAI at 24 and 52 weeks
8. Cost-effectiveness of subcutaneous over oral methotrexate measured using service utilisation at week 52
9. Treatment acceptability assessed using qualitative interviews, BMQ and TFAQ at 4-8 weeks and 24-32 weeks

Completion date
31/01/2027

Eligibility

Key inclusion criteria
1. Age ≥18 years
2. Meets American College of Rheumatology/European League Against Rheumatism (ACR /EULAR) classification criteria for RA
3. Active RA defined as at least one swollen joint assessed by a rheumatologist
4. Willing to initiate methotrexate
5. RA not treated with methotrexate previously

6. Disease Activity Score 28-joints including C reactive protein (DAS-28-CRP) ≥2.6 (blood test from initial clinic visit to be used to calculate this score at baseline visit)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
100 years

Sex
All

Total final enrolment
388

Key exclusion criteria
1. RA previously treated with other disease-modifying anti-rheumatic drugs. Patients treated with hydroxychloroquine for palindromic RA or autoantibody-positive arthralgia are eligible.
2. Psoriasis or other immune-mediated inflammatory conditions such as inflammatory bowel disease, ankylosing spondylitis, lupus, polymyalgia rheumatica or giant cell arteritis
3. Dementia, severe psychological disturbance i.e. mental health illness that makes receiving study information and initial screening questions a stressful experience,
4. Unable to give informed consent or comply with study procedures
5. Cancer treatment i.e. surgery, radiotherapy, immunotherapy or chemotherapy in the last 12 months; (current or past non-metastatic melanoma and skin cancer are eligible).
6. Solid organ transplant on long-term daily prednisolone and/or other immunosuppressive treatments
7. Stage 4/5 chronic kidney disease (CKD), chronic liver disease (e.g. autoimmune hepatitis, primary sclerosing cholangitis, hepatitis B or C, cirrhosis); low-dose methotrexate contraindicated
8. Pregnant or breastfeeding
9. Planning to become pregnant or breastfeed within the next 18 months
10. For men, intending to start a family within the next 18 months
11. Life expectancy less than 12 months

Date of first enrolment
29/09/2023

Date of final enrolment
31/05/2025

Locations

Countries of recruitment
United Kingdom

Study participating centre
Not provided at time of registration
-
NO COUNTRY SPECIFIED, assuming England
England
-

Sponsor information

Organisation
University of Nottingham

ROR
https://ror.org/01ee9ar58

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care 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 this trial will be available to researchers upon request from the NCTU (ctu@nottingham.ac.uk), a minimum of 12 months after the publication of this 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 de-identified which may impact the reproducibility of published analyses.

De-identified individual participant data will be shared with researchers external to the trial research team in accordance with the NCTU's data sharing Standard Operating Procedure wherein the request is considered by a data sharing committee which includes the CI and the sponsor. Our research grant includes costs for future data sharing to cover anonymization and extraction to allow for external research access to data.

Participants are made aware that their data is anonymised. In the informed consent form we have included the following statement so any participants entering the study will need to agree to the future use of their anonymised data 'I understand that the anonymised information collected about me may be used to support other research in the future and may be shared with other researchers.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		12/11/2025	18/11/2025	Yes	No
Protocol file	version 2.0	12/06/2024	17/03/2025	No	No
Protocol file	version 3.0	07/05/2025	08/10/2025	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes