ISRCTN32090559 https://doi.org/10.1186/ISRCTN32090559

Oral versus intramuscular glucocorticoids in rheumatoid arthritis

Submission date
26/11/2024

Recruitment status
Recruiting

Registration date
04/02/2025

Overall study status
Ongoing

Last Edited
16/07/2025

Condition category
Musculoskeletal Diseases

[X] Prospectively registered
[_] 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) causes joint pain and swelling affecting people's daily activities and quality of life. The National Institute for Health and Care Excellence advise treatment with drugs called anti-rheumatic medicines, but they can take up to 6 months to work. Whilst waiting for these medicines to take effect, patients are offered another type of drug, steroids, which act quickly to control symptoms. Unfortunately, steroids have long-term side effects such as diabetes, weight gain and skin changes, so should only be used for short periods of time. Steroids can be given as an injection into the muscle or as a daily tablet. Doctors currently do not know whether it matters which of these and what dose has the best balance between side effects and rapid symptom relief.
The LEADER trial aims to find the most effective and safest way of using steroids for patients with uncontrolled RA who are starting a new anti-rheumatic medicine.

Who can participate?
To join this study, participants must be 18 or older and have rheumatoid arthritis that meets specific criteria. They should have active disease with at least 3 tender and 3 swollen joints. Participants must be planning to start, switch, or increase their medication for rheumatoid arthritis. They need to be open to being assigned to any treatment group in the study and must be able to give informed consent.

What does the study involve?
The trial will compare 4 different doses/ways of taking steroids: 1) higher dose steroid tablets that reduce in dose over six weeks, 2) lower dose steroid tablets that reduce in dose over four weeks, 3) a one-off higher dose steroid injection or 4) a one-off lower dose steroid injection. Participants will be assessed regularly during the first 3 months and at 6 months to see how the treatment has affected their symptoms. The trial will compare how active the RA is, between tablets and injection and also dose levels, to find out which treatment is most effective.
The trial will also look at what impact the different doses and ways of taking steroids have on fatigue, ability to do day-to-day activities and work, quality of life, the amount of pain killers used and value for money to the NHS. Side effects such as weight gain and mood changes will be assessed and an at-home finger-prick blood sample will test if the steroid has affected the ability to produce a key hormone that controls the body's stress response and blood pressure.

What are the possible benefits and risks of participating?
Benefits:
Not provided at time of registration
Risks:
The LEADER trial is comparing different routes of administration and regimes that are commonly used for standard care treatment. The IMPs (oral prednisolone tablets and intramuscular methylprednisolone) are being used in the LEADER trial within their licensed indications and have well established safety profiles. The prescribing and dispensing of all IMPs will follow usual practice at participating sites. Treatment is therefore comparable with standard medical care.
Burdens: One extra visit, Completion of weekly pain VAS, Longer standard of care visits, Completion of questionnaires
Completion of finger prick blood test at home.
Extra blood needed for the trial is being collected at the same time of routine blood when ever possible, so only 1 additional blood draw will be needed - at the week 2 visit which is an additional visit for the study only.

Where is the study run from?
University of Manchester (UK)

When is the study starting and how long is it expected to run for?
November 2024 to March 2027

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

Who is the main contact?
leader@ndorms.ox.ac.uk

Study website
https://leader.octru.ox.ac.uk/

Contact information

Type(s)
Public, Scientific

Contact name
Dr Anne Francis

Contact details
Botnar Institute for Musculoskeletal Sciences, Windmill Road
Oxford
United Kingdom
OX3 7LD
+44 1865 01865 612701
leader@ndorms.ox.ac.uk

Type(s)
Principal Investigator

Contact name
Dr James Bluett

Contact details
1.204 AV Hill, Oxford Road
Manchester
United Kingdom
M13 9PT
+44 1612751614
james.bluett@manchester.ac.uk

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1010280

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
R130178, CPMS 57018

Study information

Scientific Title
The clinical and cost effectiveness of oraL vErsus intrAmuscular glucocorticoiDs in rhEumatoid aRthritis

Acronym
LEADER

Study objectives
Primary objective:
To compare the mean DAS(CRP)-28 over 12 weeks in adult patients with active RA commencing IM or oral short-term bridging GC therapy who are initiating, escalating or switching DMARD therapy.

Secondary objectives:
1. To compare the effect of:
1.1. Two IM GC dose regimens on mean DAS(CRP)-28, American College of Rheumatology (ACR) response, and EULAR Modified Boolean remission over 24 weeks.
1.2. Two PO GC dose regimens on mean DAS(CRP)-28, ACR response, and EULAR Modified Boolean remission over 24 weeks.
1.3. Oral and IM GC on analgesic use.
1.4. Oral and IM GC on patient-reported outcomes.
1.5. Oral and IM GC on toxicity.
1.6. Oral and IM GC on cumulative GC dose.

2. To conduct an economic evaluation.
3. To assess GC bridging therapy acceptability.
4. To conduct a qualitative study of GC bridging therapy acceptability.
5. To conduct a qualitative study of patients who decide not to take part during the pilot phase to explore their views and perspectives of non-participation to identify barriers to recruitment.
6. To conduct a qualitative study of healthcare professionals to explore their experiences and views of delivering LEADER and recruitment and retention of trial participants.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 03/02/2025, Leicester Central Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 2071048227 ; leicestercentral.rec@hra.nhs.uk), ref: 24/EM/0277

Study design
Interventional assessor blinded randomized parallel group controlled trial

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Safety, Efficacy

Participant information sheet

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

Interventions
Arm A (PO30) Oral glucocorticoid (prednisolone) tablets. Starting dose of 30 mg once daily tapered down after each week over 5 weeks to 5 mg once daily. Total treatment duration is 6 weeks.

Arm B (PO15) Oral glucocorticoid (prednisolone) tablets. Starting dose of 15mg once daily tapered down after each week over 3 weeks to 5mg once daily. Total treatment duration is 4 weeks.

Arm C (IM120) One-off 120mg intramuscular glucocorticoid injection (methylprednisolone). Treatment duration is 1 day.

Arm D (IM80) One-off 80mg intramuscular glucocorticoid injection (methylprednisolone). Treatment duration is 1 day.

Each participant will be followed up for 24 weeks from randomisation, with in-person appointments at Weeks 2, 4, 8, 12 and 24. The follow-up schedule is the same across all four trial arms.

The participant randomisation process will be completed online using a randomisation tool embedded within the trial database.

Intervention Type
Drug

Pharmaceutical study type(s)
Dose response, Pharmacoeconomic

Phase
Phase III

Drug/device/biological/vaccine name(s)
Prednisolone, methylprednisolone

Primary outcome measure
DAS(CRP)-28 - disease activity at Baseline, Weeks 2, 4, 8, 12

Secondary outcome measures
1. Disease activity is measured using EULAR Boolean remission and ACR20/50/70 at Baseline, Weeks 2, 4, 8, 12 and 24; and using DAS(CRP)-28 at Baseline, Weeks 2, 4, 8 and 12.
2. Patient-reported outcomes are measured using FACIT, VAS (pain), RA-QoL, WPAI, and HAQ-DI at Baseline, Weeks 2, 4, 8, 12, and 24; pain is measured weekly from Baseline to Week 24.
3. Analgesic use is measured by collecting patient's analgesic usage at Baseline, Weeks 2, 4, 8, 12, and 24.
4. Toxicity is measured using an early morning cortisol suppression at Week 12; collecting a GTI (glucocorticoid toxicity index) at Baseline, Weeks 12 and 24; collecting adverse events of special interest (AESIs) at Weeks 12 and 24; and by assessing for skin changes at injection site (IM arms only) at Weeks 2, 4, 8, 12 and 24.
5. Cumulative dose is measured by two methods: first, by collecting data from patient's medical notes on their GC dose prescribed, collected at Baseline, Weeks 2, 4, 8, 12, and 24; and secondly, by collecting data on patient's GC adherence to treatment allocation, collected from
(i) Oral Arm participants weekly from Baseline to Week 24 via participant-reported steroid diaries, and
(ii) from IM Arm participants at Baseline, Weeks 2, 4, 8, 12 and 24 via participant's medical notes.
6. Economic evaluation is measured using a healthcare resource utilisation questionnaire at Baseline, Weeks 2, 4, 8, 12, and 24; EQ-5D-5L at Baseline, Weeks 4, 12 and 24; and collecting Medication usage at Baseline, Weeks 2, 4, 8, 12 and 24.
7. Therapy acceptability to patients is measured using TFA at Weeks 12 and 24; BMQ-specific at Baseline, Weeks 12 and 24; and interviews and/or focus groups post-Week 24.
8. Barriers to recruitment are measured using 1:1 interviews with patients who decline participation during the first 9 months of recruitment.
9. Experience and views of healthcare professionals are measured using 1:1 interviews and/or focus groups from the start of recruitment to the end of the trial.

Overall study start date
22/11/2024

Completion date
31/03/2027

Eligibility

Key inclusion criteria
1. Aged 18 years or over
2. Diagnosed with rheumatoid arthritis that either currently or historically fulfils 2010 ACR /EULAR RA classification criteria
3. Active disease defined as ≥3 tender and ≥3 swollen joints
4. Planning on initiating/switching to/escalating to a conventional synthetic (cs), biologic (b) or targeted synthetic (ts) DMARD
5. Willing and able to accept either trial arm allocation
6. Willing and able to give informed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
448

Key exclusion criteria
1. Oral, intramuscular or intra-articular glucocorticoid therapy within the past 3 months
2. Glucocorticoid therapy contraindicated (as determined by treating clinician)
3. Diagnosed within the last 6 months with fibromyalgia or chronic widespread pain
4. Known to be pregnant or female patient trying to conceive
5. Unstable or uncontrolled diabetes
6. Participating or planning to participate in another interventional clinical study/trial during the study period that in the opinion of the Investigator could affect LEADER outcomes
7. Any other severe concomitant disease that, in the opinion of the investigator, might interfere with trial procedures and/or assessments

Date of first enrolment
04/07/2025

Date of final enrolment
30/06/2026

Locations

Countries of recruitment
United Kingdom

Study participating centre
Pennine MSK Partnership Ltd
Integrated Care Centre
New Radcliffe Street
Oldham
United Kingdom
OL1 1NL

Study participating centre
Derriford Hospital
Derriford Road
Derriford
Plymouth
United Kingdom
PL6 8DH

Study participating centre
Worthing Hospital
Lyndhurst Road
Worthing
United Kingdom
BN11 2DH

Study participating centre
Eastbourne District General Hospital
Kings Drive
Eastbourne
United Kingdom
BN21 2UD

Study participating centre
King's College Hospital
Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
Whiston Hospital
Warrington Road
Prescot
United Kingdom
L35 5DR

Study participating centre
Rochdale Infirmary
Whitehall Street
Rochdale
United Kingdom
OL12 0NB

Study participating centre
Fairfield General Hospital
Rochdale Old Road
Bury
United Kingdom
BL9 7TD

Sponsor information

Organisation
University of Manchester

Sponsor details
2nd Floor Christie Building, Oxford Road
Manchester
England
United Kingdom
M13 9PL
+44 161 2752725
clinicaltrials@manchester.ac.uk

Sponsor type
University/education

Website
http://www.manchester.ac.uk/

ROR
https://ror.org/027m9bs27

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

Publication and dissemination plan
Peer reviewed scientific journals
Conference presentation
Publication on website
Other

Intention to publish date
31/03/2028

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from the Chief Investigator and in accordance with the data sharing policies of OCTRU, the Sponsor and funder(s).

IPD sharing plan summary
Available on request