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Steroid-Reducing Options for ReLapsING PMR (STERLING-PMR)

Submission date
16/05/2023

Recruitment status
Recruiting

Registration date
05/10/2023

Overall study status
Ongoing

Last Edited
03/02/2026

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
Polymyalgia rheumatica (PMR) is an inflammatory disease affecting older people that causes pain and stiffness in the muscles in the shoulders, neck, hips and thighs. It is treated with (cortico)steroid medication. As the steroid dose reduces, symptoms may return or worsen (relapse), needing an increase in dose. Steroid treatment often lasts over 2 years; long-term steroids have serious health risks and the best indicator of these risks is the total (cumulative) steroid dose given throughout the illness. Some patients are referred to rheumatology; these patients are often prescribed additional medications called DMARDs (such as methotrexate [MTX] or leflunomide [LEF]), which help control inflammation and reduce the need for steroids. However, only 6% of NHS patients are given MTX and even fewer are given LEF. With regular blood monitoring, DMARDs are very safe and do not have the same long-term toxicity that steroids do. The aim of this study is to find out whether there is an added benefit of DMARDs in relapsing PMR.

Who can participate?
Patients aged 18 years and over with PMR who have relapsed at least once in the past

What does the study involve?
All patients will continue gradual steroid reduction guided by their GP. Half of them, chosen at random, will also start MTX (this can be switched to LEF if there are side effects from MTX). The researchers will follow up patients for 18 months. Every month, they will ask participants to record their current steroid dose using a questionnaire. Every 3 months they will complete extra questionnaires about their health and their use of healthcare services. The researchers will calculate the total amount of steroid taken over 18 months and compare the group allocated to DMARD to the group not allocated to DMARD. They will also test whether adding DMARD controls PMR better and improves the chances of stopping steroids. Health economic analysis will help the researchers understand whether everything involved in prescribing DMARD for relapsing PMR would be a cost-effective and viable approach for the NHS.

What are the possible benefits and risks of participating?
The researchers have designed the study to reflect good clinical practice and the latest guidelines on how to treat PMR. The study team at the hospital have been selected for their

expertise and knowledge about PMR and its treatment. It is hoped that by taking part, participants will receive the best of both worlds – good GP care and good hospital care. By taking part, they will also contribute to raising awareness and improving medical and scientific knowledge about PMR. This is very valuable in itself, because so few research studies have been done into PMR compared to other rheumatic conditions.
There will be four hospital visits and seven follow-up phone calls as part of taking part in the study. Using phone calls to maintain communication with the participants will minimise the burden of attending clinical visits at the secondary care site.
Patients may experience some side effects that could be deemed mild or more serious. A list of the known side effects of the study drugs are highlighted in the Patient Information Sheet. Patients will be having DMARD monitoring blood tests on a regular basis and therefore will be monitored very closely. Many drug interactions noted in the Summary of Product Characteristics (SmPC) relate principally to high-dose MTX, rather than the low-dose MTX used in this study and in standard rheumatology practice. The SmPC is generic, so it has not been updated recently. There is new research to indicate liver and lung problems are early and short-lived, and long-term effects are highly unusual, and the latest data will be used to help inform decisions alongside the SmPC.
There are monthly steroid use questionnaires and eight health economic/quality of life questionnaires for the participant to complete. Patients living with PMR confirmed that short and long-term health-related quality of life was a key consideration in their own decision-making around their own PMR treatment. They advised that monthly patient-reported outcomes (in the form of questionnaires) would not be excessively burdensome.
There are blood samples required as part of the study. The blood required for all the different tests will be taken in one blood sample per visit. The aim is to minimise the number of samples taken, to minimise discomfort to the patient.
Patients will be monitored frequently and will also have the contact details of the secondary care site so they can make contact with queries or concerns. If methotrexate is not tolerated by the participant, their dose can be reduced or they can be switched to leflunomide to potentially help minimise the side effects of treatment. If leflunomide is not tolerated, participants will stop taking DMARD altogether and will continue with usual care (steroid treatment only).
As part of the study, participants may undergo X-ray imaging of the chest at screening, although imaging obtained within the preceding 6 months is acceptable if no evidence of interstitial lung disease, tuberculosis or active infection was observed. Exposure to radiation can cause cancer, which usually takes some years to develop. For a 50-60-year-old individual in normal health, the estimated lifetime risk of developing cancer through taking part in the study is 1 in 900,000. The risk decreases with age.

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

When is the study starting and how long is it expected to run for?
May 2023 to April 2028

Who is funding the study?
Health Technology Assessment Programme (UK)

Who is the main contact?
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Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2023-000130-15

Integrated Research Application System (IRAS)
1005826

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
RR20/137270, IRAS 1005826, CPMS 57926

Study information

Scientific Title
Steroid-Reducing Options for ReLapsING PMR (STERLING-PMR): a multi-centre, Phase III, parallel-group, open-label, randomised controlled trial to compare the clinical and cost-effectiveness of adding immunosuppression to steroid-tapering treatment for patients with relapsing PMR, versus steroid-tapering alone

Acronym
STERLING-PMR

Study objectives
Primary objective:
To determine the clinical and cost-effectiveness of adding a disease-modifying antirheumatic drug (DMARD) to standard steroid-tapering treatment in patients with PMR who have relapsed during steroid taper. The primary objective is to determine whether, for patients with relapsing PMR, adding 18 months of DMARD therapy to usual care steroid-tapering reduces patient-reported cumulative steroid dose, compared with usual care steroid-tapering alone.

Secondary objectives:
1. To assess the impacts over 18 months of adding DMARD to steroids, by comparing treatment groups for:
1.1. PMR symptom severity (PMR-IS and sub-domains)
1.2. Health-related quality of life (EQ-5D-5L)
1.3. PMR activity score (PMR-AS)
1.4. Time to steroid cessation
1.5. Steroid-free remission at 18 months
1.6. Time to PMR relapse and number of PMR relapses
1.7. Cumulative steroid dose prescribed
2. Safety:
2.1. Adverse events of special interest related to investigational medicinal products or PMR
2.2. Serious adverse events and SUSARs
2.3. Glucocorticoid toxicity
2.4. Diagnosis of adrenal insufficiency
2.5. Time to diagnosis of GCA
3. To estimate cost-effectiveness over 18 months post-randomisation via a within-trial analysis and the long-term impact of the treatment options using a decision analytical model assessed from the NHS perspective
4. To estimate the impact of the adoption of the intervention on rheumatology service capacity

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 04/10/2023, NHSBT Newcastle Blood Donor Centre (Holland Drive, Newcastle upon Tyne, NE2 4NQ, United Kingdom; +44 207 104 8141; leedswest.rec@hra.nhs.uk), ref: 23/YH/0123

Study design
Open randomized controlled parallel-group trial

Primary study design
Interventional

Study type(s)
Efficacy, Safety

Health condition(s) or problem(s) studied
Polymyalgia rheumatica (PMR)

Interventions

The NIHR Health Technology Assessment Programme has a long-standing collaboration with the Australian National Health Medical Research Council (NHMRC) inviting collaborative international research proposals to address shared research priorities. As such, a collaborative trial is running in Australia alongside STERLING-PMR. Participating sites within the UK will be sponsored by the University of Leeds. Australian sites will be sponsored by the University of Adelaide, Chief Investigator Dr Catherine Hill.

TRIAL ARMS & TREATMENT:
Patients will be randomised in a 1:1 allocation ratio to receive either usual care alone or usual care plus DMARD. Usual care for PMR includes a long-term tapering course of steroid therapy, prescribed by their GP, alongside any concomitant medications that may be clinically indicated to prevent or manage steroid side effects.

DMARDs
Methotrexate (MTX) 2.5 mg tablets – dose range is 7.5-25 mg (starting dose 10-15 mg), frequency is taken weekly, administration route is orally, and duration is anticipated to be 18 months from baseline visit, but can be stopped in the event of toxicity. Folic acid is co-prescribed alongside MTX at a minimum 5 mg, and taken up to 6 days a week (usually not taken on the day MTX is taken) for as long as MTX is taken.
Leflunomide (LEF) 10 mg or 20 mg tablets – dose range is 10-20 mg (starting dose is 10 mg), frequency is taken daily or if not tolerated reduced to every 2 days, then twice weekly, administration route is orally, and duration will commence after stopping MTX until the final study visit at 18 months.
LEF is only taken if MTX is not tolerated, if LEF is not tolerated, DMARDs will be stopped.

RANDOMISATION PROCESS:
Randomisation will use a minimisation algorithm incorporating a random element, with minimisation factors for secondary care site, sex, number of previous relapses and steroid dose prior to last relapse (5 mg or less, or greater than 5 mg prednisolone-equivalent dose).

UK FOLLOW-UP ACTIVITY:
1. 4 in-person visits (eligibility screening, baseline, week 24 and week 80)
2. Telephone assessment at weeks 4, 8, 12, 36, 48, 60 and 72
3. Steroid use questionnaire every 4 weeks
4. Additional questionnaire pack every 12 weeks, including symptom questionnaire and health resource use
5. DMARD monitoring blood tests. The suggested guideline is blood count and liver function tests every 2 weeks until on stable DMARD dose for 6 weeks, followed by monthly for 3 months, and then quarterly (every 3 months) thereafter

AUSTRALIAN FOLLOW-UP ACTIVITY
1. 7 in-person visits (eligibility screening, baseline, week 12, week 24, week 36, week 48 and week 80)
2. Telephone assessments at weeks 4, 8, 60 and 72
3. Steroid use questionnaire every 4 weeks
4. Additional questionnaire pack every 12 weeks, including symptom questionnaire and health resource use
5. DMARD monitoring blood tests. The suggested guideline is blood count and liver function tests every 2 weeks until on stable DMARD dose for 6 weeks, followed by monthly for 3 months, and then quarterly (every 3 months) thereafter

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Methotrexate, leflunomide

Primary outcome(s)
Mean participant-reported cumulative prednisolone dose between randomisation and 18 months post-randomisation, reported by participants via a monthly questionnaire.

Key secondary outcome(s))
1. PMR symptom severity measured using the PMR-Impact Scale at weeks 0, 12, 24, 36, 48, 60, 72, 80 post-randomisation
2. Health-related quality of life measured using mean EQ-5D-5L Utility at weeks 0, 12, 24, 36, 48, 60, 72, 80 post-randomisation
3. PMR disease activity measured using mean PMR Activity Score (PMR-AS) at weeks 0, 24 and 80 post-randomisation
4. Time to steroid cessation evaluated at 18 months (can occur at any point). Time to steroid cessation, will be defined as the duration between date of randomisation and date at which participants report a current steroid dose of zero and there is sustained discontinuation of all steroids. Sustained discontinuation of steroids will be defined as not taking any further steroids for the duration of follow-up. The data to assess this will be collected via participants completing a 'Steroid Use Questionnaire' every four weeks, documenting their steroid doses over each of the preceding four weeks.
5. Time to steroid-free remission evaluated at 18 months (can occur at any point). Where participants report a current oral steroid dose of zero a decision as to whether or not steroid-free remission is achieved will be agreed between the participant and physician at the week 80 assessment. The steroid-dose of zero will be collected via participants completing a 'Steroid Use Questionnaire' every four weeks, documenting their steroid doses over each of the preceding four weeks.
6. Time to PMR relapse evaluated at 18 months (can occur at any point). Time to PMR relapse will be defined as the duration between randomisation and date of first PMR relapse. PMR relapse, which will be participant reported, will be defined as an increase in PMR symptoms sufficiently severe to require alteration of the steroid dosing plan. Participants will be asked every month via the Steroid Use Questionnaire whether they have had to adjust their planned steroid dosing plan due to an increase in PMR symptoms (patient reported relapse).
7. Number of PMR relapses evaluated at 18 months (can occur at any point). PMR relapse will be defined as an increase in PMR symptoms sufficiently severe to require alteration of the steroid dosing plan. The count of the number of PMR relapses will be derived as the sum of all relapses over the time at risk. Time at risk will be defined as the duration between date of randomisation and the earliest of date of end of follow-up, death or withdrawal.
8. Cumulative prednisolone equivalent dose prescribed, evaluated at 18 months. The total amount of oral steroid prescribed during the trial will be assessed from GP records of all prednisolone prescriptions issued during the trial.
9. Safety evaluated at 18 months (can occur at any point):
9.1. Adverse events (AEs) of Special Interest reported over 18 months post-randomisation, including those relevant to PMR and/or the investigational medicinal product
9.2. Serious adverse events (SAEs) and SUSARs regardless of relationship to PMR or

investigational product, reported over 18 months post-randomisation
9.3. Glucocorticoid toxicity, defined as per the OMERACT Glucocorticoid Core Domain Set (infection, diabetes, hypertension, fracture) adapting measures from the Glucocorticoid Toxicity Index
9.4. Time to development of GCA (defined as rheumatologist-confirmed and treated according to GCA treatment protocols specified in the 2020 BSR guideline, without the diagnosis later being revised from GCA during the 18-month period) will be defined as the duration between randomisation and date of GCA diagnosis. Participants who are not diagnosed with GCA during follow-up with be censored at 18 month, or else at the date of death or withdrawal
10. Proportion of participants diagnosed with adrenal insufficiency, evaluated at 18 months. The proportion of participants who are identified as diagnosed with adrenal insufficiency will be the proportion of participants who either have a low value of 9 am cortisol test, or an intermediate value followed by a positive short synacthen test, at any point during follow-up. Adrenal insufficiency screening tests (9 am cortisol) will be conducted within the trial but confirmation of physician diagnosis of adrenal insufficiency, will be recorded, along with the relevant date and actions taken in response.
11. Deaths from all causes over 18 months post-randomisation. Date of death will be recorded, and time to death will be derived as days from randomisation to death

Completion date
30/04/2028

Eligibility

Key inclusion criteria
1. Consent to participate (written, informed consent or witnessed verbal informed consent)
2. ALL of:
2.1. Documented diagnosis of PMR, confirmed by the local investigator
2.2. Previous steroid-responsive bilateral ache in the region of the trapezius, shoulder or upper arms, as reported by the patient to the secondary care site research team
2.3. Previous C-reactive protein (CRP) greater than 5 mg/L, or erythrocyte sedimentation rate (ESR)/plasma viscosity above local laboratory reference range, at either diagnosis or at time of a flare of PMR
3. At least 4 points from a possible 6:
3.1. Previous stiffness in association with other features of PMR, as reported by the patient to the secondary care site research team: 2 points
3.2. Previous aching of hip area (groin, buttock, lateral hip or upper thigh) in association with other features of PMR, as reported by the patient to the secondary care site research team: 1 point
3.3. Rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA/anti-CCP) both within local laboratory reference range at or during the 1 year prior to the screening visit: 2 points
3.4. No rheumatologist-documented hand or foot synovitis during active PMR symptoms: 1 point
4. Currently taking steroid treatment for PMR and willing to attempt dose reduction (tapering), as reported by the patient to the secondary care site research team
5. At least one previous relapse during steroid therapy, defined as steroid-responsive recurrence of PMR symptoms (aching in hip and/or shoulder areas), as reported by the patient to the secondary care site research team
6. Age 18 years or more at the time the consent form is signed
Footnote 1: Acceptable documentation may include but not be limited to referral

documentation from the GP practice, GP records containing diagnostic code (e.g. Read code, SNOMED code), or letter from an appropriately trained and qualified physician documenting the diagnosis

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
99 years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Contraindication to tapering steroid dose, or to methotrexate therapy
2. Women who are currently pregnant or lactating or planning to become pregnant in the next 2 years
3. Women of child-bearing potential (WCBP) or men unwilling to use an effective birth control measure (Appendix 2) whilst receiving treatment (either methotrexate or leflunomide) and for an appropriate period after the last dose of protocol treatment (6 months in the case of methotrexate, applicable for both male participants and women of childbearing potential [WCBP]). In the case of male participants the contraceptive measures can be taken by either themselves or their female partners
4. A medical condition other than PMR that has required >2 courses of systemic glucocorticoid treatment lasting 5 days or more, or any course lasting 30 days or more, during the year prior to randomization
5. Giant cell arteritis (previous or current)
6. Rheumatoid arthritis, psoriatic arthritis or spondyloarthritis (previous or current)
7. At the baseline visit active infection of sufficient severity to be a contra-indication to commencing methotrexate
8. Treatment with trimethoprim or trimethoprim-sulfamethoxazole (co-trimoxazole) at the time of the baseline assessments
9. Active gastric ulcer at the baseline visit
10. Known prior history of a significant immunodeficiency syndrome, defined as an immunodeficiency severe enough to cause recurrent infections of sufficient frequency or severity to preclude DMARD treatment
11. Known prior history of hereditary galactose intolerance, hereditary total lactase deficiency or hereditary disorder of glucose-galactose malabsorption
12. Other medical condition that is severe enough to seriously compromise evaluation of the

primary or key secondary endpoints
13. Treatment with any immunosuppressive therapy (conventional synthetic, targeted synthetic or biological DMARD) within 3 months prior to randomisation
14. Treatment with any investigational drug in the last 4 months prior to the start of protocol treatment
15. Unable to complete essential study procedures and communicate with study staff independently
16. Participants must NOT fulfil any of the following within 6 weeks prior to baseline: Haemoglobin <10.0 g/dL; total white cell count <3.5 x 10e9/L; absolute neutrophil count <1.5 x 10e9/L; platelet count <100 x 10e9; ALT (alanine aminotransferase) or AST >2 x upper limit of reference range for the laboratory conducting the test, eGFR (estimated glomerular filtration rate) <30 ml/min
17. Evidence of respiratory disease on chest radiograph (performed during screening or within the 6 months prior to screening) of sufficient severity to be a contra-indication to commencing methotrexate

Footnote 2: Contraindication to MTX includes comorbidities such as severe respiratory disease or chronic infections.

Date of first enrolment
25/01/2024

Date of final enrolment
31/10/2026

Locations

Countries of recruitment
United Kingdom

England

Wales

Australia

Study participating centre
Chapel Allerton Hospital
Harehills Lane
Leeds
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LS7 4RB

Study participating centre
Norfolk & Norwich University Hospital
Colney Lane
Colney

Norwich
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Study participating centre
Basildon University Hospital
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SS16 5NL

Study participating centre
Southend University Hospital
Prittlewell Chase
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SS0 0RY

Study participating centre
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Fairmile Road
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BH23 2JX

Study participating centre
Torbay Hospital
Lowes Bridge
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TQ2 7AA

Study participating centre
Royal Cornwall Hospital
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TR1 2JA

Study participating centre
Luton and Dunstable University Hospital
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LU4 0DZ

Study participating centre
James Cook University Hospital
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TS4 3BW

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LA1 4RP

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Study participating centre
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Sponsor information

Organisation
University of Leeds

ROR

https://ror.org/024mrxd33

Organisation
University of Adelaide

ROR
https://ror.org/00892tw58

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, Health Technology Assessment (HTA), HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request. De-identified individual participant data datasets generated and/or analysed during the current study will be available upon request from the Clinical Trials Research Unit, University of Leeds (contact CTRU-DataAccess@leeds.ac.uk in the first instance). Data will be made available at the end of the trial, i.e. usually when all primary and secondary endpoints have been met and all key analyses are complete. Data will remain available from then on for as long as CTRU retains the data.
CTRU makes data available by a 'controlled access' approach. Data will only be released for legitimate secondary research purposes, where the Chief Investigator, Sponsor and CTRU agree that the proposed use has scientific value and will be carried out to a high standard (in terms of scientific rigour and information governance and security) and that there are resources available to satisfy the request. Data will only be released in line with participants' consent, all applicable

laws relating to data protection and confidentiality, and any contractual obligations to which the CTRU is subject. No individual participant data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention, usually stipulating that data recipients must delete their copy of the released data at the end of the planned project.
The CTRU encourages a collaborative approach to data sharing, and believes it is best practice for researchers who generated datasets to be involved in subsequent uses of those datasets. Recipients of trial data for secondary research will also receive data dictionaries, copies of key trial documents and any other information required to understand and reuse the released datasets.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes