STERLING-PMR Protocol Synopsis v1.0 08/11/2023

Trial Title	STEeroid-Reducing Options for ReLapsING PMR (STERLING-PMR): a pragmatic, randomised trial to compare the clinical and cost-effectiveness of adding immunomodulation to steroid-tapering treatment for patients with relapsing PMR, versus steroid-tapering alone.
Short title	STERLING-PMR
Protocol Number	V3.0 18/08/2023
Clinical Phase	Phase III
Trial Design	Multi-centre, Phase III, parallel-group, open-label, randomised controlled trial with internal pilot. Patients will be randomised in a 1:1 allocation ratio to receive either usual care alone or usual care plus DMARD.
Trial Participants	Patients with polymyalgia rheumatica (PMR) who are (1) receiving steroid treatment and (2) who have previously experienced at least one relapse of PMR.
Inclusion Criteria	Patients must fulfil ALL of the following: 1. Age 18 years or more at the time the consent form is signed. 2. ALL of: (i) documented[1] diagnosis of PMR, confirmed by the local investigator. (ii) 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. (iii) previous C-reactive protein (CRP) greater than 5mg/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: • Previous stiffness in association with other features of PMR, as reported by the patient to the secondary care site research team: 2 points. • 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. • 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. • 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. Consent to participate (written, informed consent or witnessed verbal informed consent). [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.

Exclusion criteria	**Patients will be excluded from this study for ANY of the following reasons:** 1. Contraindication to tapering steroid dose, or to methotrexate therapy[2] 2. Women who are currently pregnant, 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 whilst receiving treatment (methotrexate or leflunomide) and for an appropriate period after the last dose of protocol treatment:(Six months in the case of methotrexate, applicable for both male participants and women of child-bearing 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 x10^9/L; absolute neutrophil count <1.5 x10^9/L; platelet count <100 x10^9; ALT (alanine aminotransferase) or AST > 2 x upper limit of reference range for the laboratory conducting the test, eGFR (estimated glomerular filtration rate) <30ml/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. [2] Contraindication to MTX includes comorbidities such as severe respiratory disease or chronic infections
Planned Sample Size	200

Planned Number of Recruiting Sites	20	
Recruitment Plan	Participants will be identified in both primary and secondary care but consented and recruited in secondary care. Each secondary care site will have a number of GP practices acting as Participant Identification Centres. Practices will be asked to search their electronic medical records to identify potentially eligible patients who, if consenting and eligible, could be recruited by the secondary care site. Patients with PMR who are already under the care of a secondary care clinical team may also be invited. They may be identified via review of patient lists or databases held by their clinicians or rheumatology departments or identified and invited during their routine clinical appointments.	
Treatment	18 months duration. Steroid prescribing and management will remain the responsibility of the participant's GP practice. DMARDs will be prescribed by the secondary care site, who will also take responsibility for DMARD monitoring blood tests.	
Follow-up schedule	4 study visits at secondary care site over 18 months (screening, baseline, 6 months, 18 months). In addition, secondary care site research teams will conduct telephone assessments with participants from both arms at weeks 4, 8, 12, 36, 48, 60 and 72. Estimated time commitments: *Screening: 40 mins research nurse time, 20 mins physician time* *Baseline: 30 mins research nurse time, 15 mins physician time* *6-month follow-up visit: 30 mins research nurse time, 5 mins physician time* *18-month follow-up visit: 30 mins research nurse time, 5 mins physician time* *Telephone assessments: 5-10 mins research nurse time/assessment* CTRU will manage the administration of monthly questionnaires sent to participant either by post or electronically. Consent will be sought for continued follow up via routinely-collected clinical data via electronic healthcare records and national datasets.	
Planned Trial Period	Recruitment period (including 12 month pilot phase): 1st October 2023 to 30th June 2025 Follow-up period: 1st July 2025 until 31st December 2026.	
	Objectives	Outcome Measures
Primary Outcome	To determine whether adding DMARD therapy to usual care steroid-tapering reduces patient-reported cumulative steroid dose over 18 months, compared with usual-care steroid tapering alone, in PMR patients who have relapsed.	Steroid dose taken by participants reported by monthly questionnaire.

Secondary Outcomes	To assess the impacts over 18 months on:	
	PMR symptom severity	Assessed quarterly by PMR-Impact Scale.
	Health-related quality of life	EQ-5D-5L
	PMR disease activity	PMR-AS assessed at 0, 6, 18 months.
	Time to stop steroids	Date of steroid cessation if reported by patient in monthly questionnaires.
	Time to steroid-free remission.	Date of steroid cessation and remission of PMR symptoms if reported by patient in monthly questionnaires.
	Time to PMR relapse	Date of patient- reported relapse: if an increase in PMR symptoms was sufficiently severe to require alteration of the steroid dosing plan.
	Number of PMR relapses	Patient-reported relapse: if an increase in PMR symptoms was sufficiently severe to require alteration of the steroid dosing plan.
	Cumulative steroid dose prescribed by GP	Total prednisolone-equivalent steroid dose prescribed by GP during trial period: collected from GP records at the end of the trial.
	Safety	Adverse events related to PMR or to trial treatment, reported directly by patients to study site. Serious adverse events (SAEs) and SUSARs regardless of relationship to PMR or investigational product reported over 18 months post randomisation Glucocorticoid toxicity Time to development of giant cell arteritis (GCA)- Date of clinical diagnosis confirmed by hospital site.

		Diagnosis of adrenal insufficiency - As per local guidelines
	Deaths	Date of death for all causes during 18 months follow-up period
	Cost-effectiveness	Resource use questionnaire (3-monthly)
	Impact of increased referrals on capacity of rheumatology services.	Health economic modelling
Blood tests at screening	FBC, U+E, LFT Rheumatoid factor and anti-CCP antibody titres	
Assessments collected at each hospital study visit (0, 6, 18 months)	Blood pressure Inflammatory markers PMR disease activity Clinical remission or non-remission status Glycaemic status Metabolic status Adrenal insufficiency	Blood pressure CRP PMR-AS (composite score) Clinician's judgement of PMR remission HbA1c Urate 9am cortisol (if pred<=5mg)
Radiology Involvement	Chest radiograph (screening)	
Laboratory Involvement	All laboratory tests will use the local hospital laboratories. No central laboratories will be involved.	
Investigational Medicinal Product(s)	All patients will continue to receive usual care (a tapering course of steroid under the care of their GP). Patients will be randomised 1:1 to disease-modifying antirheumatic drug (DMARD) therapy plus usual care, or usual care alone. For those randomised to the DMARD arm, DMARD will be prescribed by and blood monitoring tests arranged by the hospital site throughout the trial. DMARD will be methotrexate first line; this will be switched to leflunomide in case of lack of tolerance or inefficacy. Patients who successfully stop steroid during the 18-month follow-up period may if they wish stop DMARD after 6-12 months of steroid-free remission.	
Formulation, Dose, Route of Administration	Methotrexate (MTX) will be given orally, starting at 15mg weekly and escalating to 25mg weekly if tolerated, reduced to minimum 10mg weekly if not tolerated. Folic acid will be co-prescribed with MTX to reduce toxicity as per usual practice. Leflunomide (LEF) will be given orally, starting at 10mg daily and escalating to 20mg daily if tolerated, reduced to 10mg every other day if not tolerated.	

	Prescribing and blood test monitoring for MTX or LEF, according to British Society of Rheumatology Guidelines, will be undertaken by the hospital site throughout the trial (participants may attend their GP practice and/or local phlebotomy hub for blood draws where GP practice is willing and has capacity).
Statistical analysis	Primary analysis will be conducted on the intention to treat (ITT) population. Primary analysis will be conducted on log (cumulative steroid dose over 18 months) using multivariable linear regression.
Sample size calculation	Subject to assumptions about coefficient of variation, 20% attrition and 5% significance level, 200 participants will provide a 90% power to detect a target 30% reduction in cumulative prednisolone dose equivalent.