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CLINICAL TRIAL PROTOCOL

Steroid-Reducing Options for ReLapsING PMR (The STERLING-PMR study): 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

Australian Protocol Version and Date		**Version 2, 24th july2023**	
Based on UK Protocol Version and Date		**Version 1.1, 27 January 2023**	
HREC:	**2023/HRE00162**		
EudraCT Number	**2023-000130-15**	**ISRCTN**	**Pending**

THE UNIVERSITY of ADELAIDE

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3. TRIAL SUMMARY

Trial Title	Steroid-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
Clinical Phase	Phase III
Study Sites	The Queen Elizabeth Hospital / University of Adelaide The Austin Hospital The University of Western Australia / Fiona Stanley Hospital
Trial Design	Multi-centre, Phase III, parallel-group, open-label, randomised controlled trial with internal pilot. The screening period of up to 6 weeks, a 80 week open label study period. At baseline, each subject will switch from oral glucocorticoids obtained from independent sources to oral prednisolone provided by the t the equivalent dose that the subject was taking just prior to the Baseline Visit, rounded up to the nearest 1 mg The study will consist of 4 study visits at site over 18 months. In addition, site research teams will conduct telephone assessments with participants from both arms at weeks 4, 8, 12, 36, 48, 60 and 72. Participants 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.
Planned Sample Size	50 (of the 200 total)
Planned Number of Recruiting Sites	3
Follow-up schedule	7 study visits at site over 18 months (screening, baseline,12,24,36,48 and 80 weeks)) In addition, site research teams will conduct telephone assessments with participants from both arms at weeks 4, 8, , 60 and 72. CTRU will manage the administration of monthly questionnaires sent to participant either by post or electronically.

3.1 UK and Australian collaboration

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. The local sponsor will be responsible for gaining all relevant local regulatory approvals. CALHN will be the Lead site for Australia with local governance at all other Australian sites.

4. GLOSSARY OF TERMS/DEFINITIONS

Abbreviation	Explanation
ACPA	Anti-citrullinated peptide antibody
AE	Adverse event
ALT	Alanine aminotransferase
AR	Adverse reaction
AST	Aspartate aminotransferase
BP	Blood pressure
CI	Chief investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CRP	C-reactive protein
CRN	Clinical Research Network
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTRU	Clinical Trials Research Unit
DMARD	Disease-modifying anti-rheumatic drug (conventional synthetic)
DMEC	Data Monitoring and Ethics Committee
DSUR	Development Safety Update Report
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ESR	Erythrocyte sedimentation rate
FA	Folic acid
FBC	Full blood count
GCA	Giant cell arteritis
GCP	Good Clinical Practice
GP	General practitioner
HbA1c	Glycated haemoglobin test
IMP	Investigational medicinal product
INR	International normalized ratio
ISF	Investigator Site File
ITT	Intention-to-treat
LEF	Leflunomide
LFT	Liver function test
mg	Milligrams
MHRA	Medicines and Healthcare Products Regulatory Agency
MTX	Methotrexate
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OMERACT	Outcome Measures in Rheumatology Clinical Trials
PI	Principal investigator
PIC	Patient Identification Centre
PIS	Patient Information Sheet
PMR	Polymyalgia rheumatica
PMR-AS	PMR Activity Score
PMR-IS	PMR Impact Scale
PPI	Patient and public involvement
PSF	Pharmacy Site File
QoL	Quality of Life

RA	Rheumatoid arthritis
RCT	Randomised controlled trial
RDE	Remote data entry
REC	Research Ethics Committee
RF	Rheumatoid factor
RGF	NHS Research Governance Framework
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SmPC	Summary of Product Characteristics
SNOMED	Systematized Nomenclature of Medicinal Clinical Terms
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
ToR	Terms of Reference
TMG	Trial Management Group
TSC	Trial Steering Committee
ULN	Upper limit of normal
U+E	Urea and electrolyte test
VAS	Visual Analogue Scale

5. BACKGROUND

5.1 WHAT IS PMR?

Polymyalgia rheumatica (PMR) is a common, inflammatory musculoskeletal disease that predominantly affects older people. The average age of onset is around 75 years. In the UK and Australia, PMR is usually diagnosed by the ’s general practitioner (GP). The cardinal symptoms of PMR are symmetrical pain and stiffness around the shoulder and hip girdles; these symptoms are generally worse in the morning compared to the afternoon, and are exacerbated by inactivity. Patients may complain of difficulty turning over in bed, getting out of bed, rising from a chair, or putting on footwear. Biological markers of inflammation in PMR include elevation in the laboratory markers C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Research studies employing advanced imaging have revealed that the primary site of inflammation in PMR is around muscles, tendons and ligaments, with secondary bursitis, rather than being centred on the joint lining (1, 2).

Other medical conditions, such as the early stages of rheumatoid arthritis, may “mimic” PMR; therefore, in the presence of diagnostic uncertainty, specialist (rheumatology) referral is recommended to confirm or refute the diagnosis of PMR. In one UK dataset, 12.6% of patients with PMR were seen by a rheumatologist within 6 months of their PMR diagnosis (3).

The incidence of polymyalgia rheumatica (PMR) has been estimated from UK primary care data as 96 new diagnoses per 100,000 over-40s per year (4). An average-sized GP practice list of 8,500 would be expected to have 37 patients who have ever been treated for PMR, and 4.5 new PMR cases per year (4). In UK primary care, 97.7% of patients diagnosed with PMR are White, 1.2% Asian, 0.4% Afro-Caribbean and 0.8% other ethnicity (3). There is no comparable Australian data but likely to be similar prevalence here.

PMR is closely linked to giant cell arteritis (GCA), a type of vasculitis. Symptoms of GCA may include headache, jaw ache on chewing, or visual loss (5). Patients with suspected GCA should be referred immediately for specialist evaluation (6).

5.2. HOW IS PMR USUALLY TREATED?

PMR is treated with glucocorticoids (corticosteroids, “steroids”), which in the UK is typically prednisolone at a starting dose of 15-25mg daily. This usually results in rapid relief of pain and stiffness. The initial steroid dose is gradually tapered to 10mg daily; thereafter the taper continues with a 1mg reduction in daily dose every 1-2 months. This initial tapering regimen would normally result in cessation of steroid therapy at around 14 months from diagnosis, but in about 50% of patients, PMR symptoms of pain and stiffness return (relapse) during the taper, necessitating re-escalation of the steroid dose (7, 8). If PMR relapse occurs during the steroid taper, the steroid dose can often be re-escalated by the amount needed – typically an additional 2-5mg prednisolone daily - to bring PMR symptoms back under control (9, 10). After this, the taper resumes, often at a slower rate than before. This re-escalation and subsequent resumption of a slower taper prolong the treatment course, so that many patients remain on steroids far in excess of 14 months; indeed, 1 in 4 UK PMR patients take steroids for more than 4 years (4). Most patients with PMR experience some steroid side-effects during their treatment course (11); late effects include osteoporosis and fracture which may occur years after

the steroids have been stopped. Taking more than 2 years of steroids for PMR is associated with a substantially greater risk of steroid side-effects, compared to a shorter treatment duration (12)

The 2010 British Society for Rheumatology guideline for diagnosis and management of PMR suggest specialist referral of patients with relapsing PMR under certain circumstances, such as after 2 years of steroid therapy (9); the guideline directs specialists to consider starting disease-modifying anti-rheumatic drug (DMARD) therapy, such as methotrexate (MTX), after the second PMR relapse. These pragmatic suggestions were based on the limited evidence available at that time.

In 2015, PMR treatment recommendations were jointly issued by the American College of Rheumatology and the European League against Rheumatism, to consider starting MTX earlier than the 2010 British guidelines had advised. The conditional recommendation in the updated 2015 recommendations was to consider MTX early for patients with PMR *who had relapsed, were at higher risk of future relapse, had already experienced steroid side-effects or were at risk of steroid side-effects*.

This shift in the recommendations was based on five clinical studies of MTX, including four randomised trials summarised below, which together provided moderate to high evidence for the efficacy of MTX in reducing cumulative steroid requirements. However, these trials were powered for efficacy and not for steroid side-effects, and thus could not provide definitive evidence that reduction in cumulative steroid requirements translated into a significant reduction in steroid side-effects and overall health benefit; furthermore no cost-effectiveness analyses have to date been performed, with particular concerns about whether UK specialist rheumatology services have the capacity to initiate and monitor DMARD therapy in the majority of PMR patients as would be implied by the 2015 recommendations. Implementation of the 2015 recommendations in the UK remains limited, in part because NHS specialist referral criteria for PMR still reflect the older, British guideline. Public awareness of modern diagnosis and treatment of PMR also remains low and the disease carries some social stigma due to its perceived association with ageing, as well as medical stigma associated with steroid dependence. At present, most NHS patients with PMR remain in primary care, managed with steroid therapy alone. A 2021 NHS England report, *Getting it Right First Time for Rheumatology*, stated that "most cases [of PMR] can be appropriately managed in primary care." (13).

5.3 THE NEED FOR BETTER TREATMENT OPTIONS FOR PMR

Glucocorticoid ("steroid") therapy rapidly brings the pain and stiffness of PMR under control, with a corresponding improvement in physical and mental health-related quality of life compared to untreated PMR (14). However, steroid therapy has multiple unwanted effects (steroid toxicity), which accumulate over time and may not be fully reversible even after the steroid treatment has stopped (15). Older patients such as those with PMR are particularly susceptible to steroid toxicity. Patients whose duration of prednisolone therapy has been prolonged by dose-escalations related to PMR relapses are likely to be at the greatest risk of long-term steroid toxicity.

Steroid treatment for PMR confers a 63% increased risk of fracture (16), at least a twofold increased risk of diabetes(17) and a dose-dependent increased risk of infection (18). The risk of infection is related to both current and cumulative dose. Prolonged steroid therapy (daily dose of 5mg prednisolone-equivalent or greater, for 4 weeks or more) can cause adrenal insufficiency that may persist for months to a year or more after the steroid dose is tapered below 5mg daily (19)

Other outcomes of glucocorticoid therapy listed in the Outcome Measures in Rheumatology Clinical Trials (OMERACT)-endorsed Core Domain Set for adverse impacts of glucocorticoid therapy include weight gain, mood disturbance, and fatigue (20). 15% of patients with PMR are reported to experience depression (21) which is likely to represent the combined effect of the disease and the treatment.

An adjunctive treatment that could reduce steroid requirements in relapsing PMR would have the potential to substantially improve long-term physical and mental health of this patient group.

5.4 DMARD THERAPY FOR PMR

DMARDs (disease modifying antirheumatic drugs) are used in rheumatology across multiple rheumatic diseases including rheumatoid arthritis, psoriatic arthritis, and vasculitis. DMARDs act via a variety of mechanisms to reduce activation of immune cells. The three classes of DMARDs in clinical use are *conventional synthetic*, *biologic* and *targeted synthetic*. In this protocol, by "DMARDs" we refer to the class that has been in clinical use for the longest: conventional synthetic DMARDs. In rheumatoid arthritis, the paradigmatic inflammatory rheumatic disease, MTX is still considered the "anchor drug"; recent years have seen a strong movement away from routine utilisation of steroid therapy in RA due to increasing recognition of steroid toxicity, while reinforcing the key role of methotrexate (22). Over the same time period, many other inflammatory diseases of rheumatology, respiratory medicine, gastroenterology and dermatology have seen a move away from steroids and towards DMARDs as evidence has accumulated for the benefit of doing so.

PMR has been left behind in this increasing move to DMARD over steroid therapy, perhaps influenced by misconceptions of PMR as a short-term condition, coupled with the "invisibility" of patients with PMR remaining in primary care. Only 6% of NHS patients with PMR receive MTX (16). Local data from Central Adelaide Local Health Network demonstrated that 31% of patients with PMR treated by a specialist rheumatology clinic were prescribed methotrexate (23). Under current prescribing guidance, participants can only be prescribed a DMARD by their GP under a shared care agreement in which they remain under the joint care of their GP and a specialist. Since few patients with PMR are currently referred to specialist care, a shift to universal DMARD prescribing for PMR could be unachievable. A more achievable aim would be a modification of the currently existing stratified care pathway: to offer DMARD to patients with PMR that have relapsed during steroid taper, as this patient group has been shown to be at substantially higher risk of steroid toxicity (12). The validity of such a strategy has not been formally tested.

At present, the principal DMARDs initiated by UK rheumatologists for PMR are methotrexate (MTX) and leflunomide (LEF); the efficacy of MTX has been investigated in clinical trials and the first LEF trial in PMR is currently underway. MTX for new-onset PMR was investigated by two randomized, placebo-controlled trials (RCTs) of MTX (n=40, n=72) (24, 25) and two open-label trials (n=24, n=58) (26, 27). In the larger RCT (n=72), MTX reduced cumulative steroid dose and duration of steroid therapy (24). The smaller RCT (n=40) failed to show a significant benefit of MTX, but in addition to issues with under-powering and inclusion of some patients with GCA, it had a 47% dropout rate (25). Meta-analysis of the two open-label trials over 12 months showed 0.5g reduction in cumulative prednisolone dose with MTX, although they were unable to demonstrate a reduction in PMR relapse rate (28).

LEF to date has not been tested in a published RCT in relapsing PMR, but an ongoing clinical trial in new-onset PMR in an ongoing clinical trial (NCT0357679).

An unpublished survey of UK and international rheumatologists and GPs was conducted in 2019. 133/138 (96%) rheumatologists considered MTX to be an appropriate option in PMR. LEF was the next most favoured drug (51%). Most felt there was insufficient evidence about which patients would benefit from DMARD. 64/65 (98%) UK rheumatologists and 45/51 (88%) GPs agreed a robust clinical trial of MTX would alter their practice. In summary, there is general acceptance in the field of the efficacy of MTX in PMR, with LEF a second choice likely influenced by clinical experience and published case series in PMR/GCA (29, 30). However, there are limited data on the real-world effectiveness and cost-effectiveness of DMARDs in relapsing PMR, including implications for capacity within the rheumatology service should more patients with relapsing PMR be referred from primary care if current referral guidance were to change.

Participant safety is paramount in any clinical trial. Recent evidence has accumulated providing high-quality data as to the safety of MTX, as the primary DMARD to be tested in the current trial. The four trials of MTX for PMR employed MTX doses of 7.5-10 mg weekly for PMR; since those trials were conducted, in clinical practice a target dose of MTX of 20-25mg weekly is considered more appropriate and has been shown to be safe and well-tolerated in a PMR population (31). Therefore, the trials to date may have underestimated the potential benefit of MTX. With many decades of experience of prescribing MTX in daily clinical practice, significant safety events are extremely rare when usual prescribing practices are followed. Best practices for DMARD prescribing and monitoring are described in 2017 clinical guidelines from the British Society for Rheumatology (32). Since the publication of the British Society for Rheumatology guidelines, further evidence has accumulated from placebo-controlled trials as to the safety profile of MTX. In a meta-analysis of trials across all indications, adverse events were unrelated to MTX dose (33), providing reassurance that using a more modern dose of MTX is likely to be safe in this patient group. CIRT was a large RCT of MTX in older individuals with cardiovascular risk factors without chronic inflammatory diseases or taking long-term steroid therapy (n=4786 randomised), published in 2020. In CIRT, serious infections were not increased with MTX compared to placebo (34). In the pre-randomisation, active run-in phase of CIRT (n=6158), all detectable via standard laboratory tests: haematologic (21.5%), renal (18.2%), and liver (5.5%). Other adverse effects during the CIRT active run-in phase were comparatively rare. Post-randomisation, the trial quantified numerically small increases in gastrointestinal, pulmonary, infectious and haematologic adverse events, an increase in skin cancers (but not other types of cancers) and, unexpectedly, a decrease in renal adverse events in the MTX arm compared to the placebo arm (14). Given the large sample size of CIRT, its placebo-controlled design, exclusion of concomitant steroid therapy, and strict adjudication of MTX-related adverse effects, it is unlikely that the current trial will provide additional scientific data as to new safety signals for MTX.

Paradoxically, the risks of long-term steroid therapy in PMR (usual care) are arguably at least as high as those of the investigational medicinal products (MTX, LEF) being tested in this trial. 81% of patients treated with steroids along experienced adverse events during the first year of an observational study (14, 34).

PMR is a chronic inflammatory disease and so patients in the current trial would be expected to derive benefit from MTX that would not have been expected in the CIRT trial population. In the current trial, the small increase in adverse effects that would be expected from MTX therapy have to be balanced against the potential benefits of better control of PMR inflammation and reduced steroid toxicity.

This trial has been designed with patient involvement throughout. The pragmatic design of this trial reflects a desire that its results should be generalisable to the group of patients with PMR who stand to benefit the most: those at greatest risk of steroid toxicity, including older, frailer patients with multiple long-term conditions. Therefore, this trial is designed to be as inclusive as possible, and to provide them with all the support they may require to provide informed consent. The clinical trial design underwent final review by patient and public contributors by means of a three-hour workshop, held in February 2020.

From the earliest stages of trial design, patient and public contributors were supportive of the research question, which they confirmed was important to them, but needed explanation as to why a randomised design would be more robust than a purely observational study in routine care. Patient and public contributors advised that "scaremongering" about both DMARDs and steroids was common, and advised that participant-facing materials would need to be carefully designed to convey "balanced" information. This has informed the simple, visual design of the participant-facing materials, designed to encourage verbal communication between participant and study team and to communicate the key ideas of equipoise and randomisation.

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 was that monthly patient-reported outcomes (in the form of questionnaires) would not be excessively burdensome, as long as the questions were felt to be relevant to them. Patient and public contributors also suggested the idea of an additional "personal diary" that would be "owned" by the participant themselves, that could be shared with others if they chose.

Patients living with PMR had very diverse concepts of what PMR "relapse" meant to them, compared to the proposed definition based on current clinical practice that will be used as an inclusion criterion in this trial. While tapering prednisolone for PMR, patients adjust their steroid dose in response to changes in the severity of their PMR symptoms; cumulative steroid dose requirement is a key, quantifiable outcome that connects cumulative PMR disease activity and the combined effects of PMR and its treatment on health-related quality of life.

While this open-label trial is designed to be as pragmatic as possible, patients living with PMR reported substantial variation in care between different GPs, and advised that the study team might consider how they would ensure that minimum standards of care were adhered to within this trial sufficient to ensure participant safety in both trial arms, not just the DMARD arm. Since the trial was originally designed, "telemedicine" is increasingly utilised in both primary and secondary care, particularly for patients with stable disease or who find face to face medical appointments burdensome. The final trial design therefore incorporates regular scheduled telephone contact with the study team, in which adverse events can be identified and the site investigator and/or GP can be informed as appropriate.

5.6. IMPORTANCE OF THIS RESEARCH QUESTIONIN THE CONTEXT OF THE COVID-19 PANDEMIC

Observational and trial data suggest clear health economic benefits of steroid-sparing strategies in other rheumatic diseases (35, 36). We hypothesise that MTX via its anti-inflammatory effect will reduce the risk of PMR flaring during the steroid taper, and that this will consequently reduce long-term steroid exposure.

At the time of writing, the experiences of the first two years of the coronavirus pandemic have highlighted the risks of prolonged steroid exposure, especially for older patients, whose baseline infection risk is higher due to their age (37). The earliest observational data suggested that steroids, more than DMARDs, were associated with adverse outcomes in COVD-19 (38). Supporting this early impression, in patients with vasculitis and polymyalgia rheumatica, risk factors for adverse outcomes from COVID-19 infection include older age, male sex, number of comorbidities, uncontrolled disease activity and taking a daily dose of 10mg or more of prednisolone (or equivalent doses of other steroids); there was no significant increase in risk associated with the conventional synthetic DMARDs, including MTX or LEF, although the more potent DMARDs, rituximab and cyclophosphamide, were associated with greater severity of COVID-19 (39).

If the hypothesis of this trial is upheld and if conventional synthetic DMARD therapy (MTX, LEF) are effective in reducing PMR disease activity and therefore the steroid dose needed to control PMR, this would be expected to result in a net benefit to patients with PMR particularly those with other risk factors for COVID-19 severity (age, sex, comorbidity). The trial itself has been designed with the minimum possible number of hospital visits, combined with “telemedicine” phone contact, reflecting post-pandemic patterns of clinical care provision.

6. AIMS AND OBJECTIVES

6.1 AIM

To determine the clinical and cost-effectiveness of adding a DMARD to standard steroid-tapering treatment in patients with PMR who have relapsed during steroid taper.

6.2 PRIMARY OBJECTIVE

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 (prednisolone equivalent) steroid dose, compared with usual care steroid-tapering alone.

6.3 SECONDARY OBJECTIVES

Secondary objectives are:

- to assess the impacts over 18 months of adding DMARD to steroids, by comparing treatment groups for:
    - PMR symptom severity (PMR-IS and sub-domains)
    - Health-related quality of life (EQ-5D-5L)
    - PMR Disease Activity (PMR-AS)
    - time to steroid cessation
    - steroid-free remission at 18 months
    - time to PMR relapse and number of PMR relapses
    - cumulative (prednisolone equivalent) steroid dose prescribed

- Safety:
    - adverse events of special interest related to investigational medicinal products or PMR
    - serious adverse events and SUSARs
    - glucocorticoid toxicity
    - diagnosis of adrenal insufficiency
    - time to diagnosis of GCA
- 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.
- to estimate the impact of adoption of the intervention on rheumatology service capacity

6.4 EXPLORATORY OBJECTIVES

Exploratory objectives are to:

- classify symptom trajectories in relapsing PMR
- describe the characteristics of participants who switch from MTX to LEF
- explore comparative effectiveness of MTX versus LEF
- explore predictors of adverse outcomes in PMR
- describe inflammatory markers and steroid dose at time of relapse

7. TRIAL DESIGN

The trial is a, multi-centre, Phase III, parallel-group, open-label, randomised controlled trial, which plans to recruit a total of 200 participants (of which 50 are form Australia) with PMR who are currently receiving steroid therapy and have previously relapsed at least once during tapering of the steroid dose.

Participants will be randomised in a 1:1 allocation ratio to receive either usual care alone or usual care plus DMARD. Randomisation will use a minimisation algorithm incorporating a random element, with minimisation factors for sex, number of previous relapses and steroid dose prior to last relapse (5mg or less, greater than 5mg prednisolone dose equivalent).

The trial will include a 12-month internal pilot phase to evaluate the feasibility of recruitment and therefore delivery of the trial (see section 7.6).

7.1 BLINDING

Due to the nature of the DMARD treatment it is not practical to blind the participant, the clinical team or the research team to the allocated treatment group. This is because the first DMARD prescribed in the DMARD arm, MTX, is taken on a once-weekly basis and is associated with substantial variation in nausea and fatigue over the week following each administration (40).

7.2 STUDY SETTING

The study will be conducted across a local hospital at each study site.. Each Participant site will search its own database of electronic medical records to identify potentially eligible participants who, if consenting and eligible, may be recruited by the site.

Once participants have been recruited to the trial, the site will have responsibility for the planned steroid taper along with the DMARD elements of the participant's care.

CALHN will obtain Ethics under the NHMRC national mutual acceptance scheme. All sites will act as research centres and hence will need to have obtained local Governance and management approvals and undertaken site initiation training with the CALHN trial coordinator prior to commencing recruitment into the trial.

7.3 TREATMENT REGIMENS

7.3.1 Steroid management (both arms)

Participants in each arm of the trial will continue to receive usual care for their relapsing PMR, including a long-term tapering course of steroid therapy, alongside any concomitant medications that may be clinically indicated to prevent or manage steroid side-effects.

If the PMR symptoms remain well-controlled during the steroid taper without any further relapses, and the participant is able to stop taking steroid entirely, they will be able to do so just as they do in usual care.

If there is a relapse of PMR disease activity, the steroid may be re-started, or the dose may be held constant for longer than originally planned, or the dose may be escalated; as in usual care this will be individualised to the participant according to the clinical discretion of the PI.

7.3.2 Participants randomised to DMARD arm

In this trial, DMARDs will be prescribed by the site, which will also take responsibility for arranging and checking the results of DMARD monitoring blood tests, and for issuing DMARD (DMARD may be posted to the participant from site pharmacy). The allowed DMARDs will be MTX or LEF.

In addition to usual care steroid therapy, participants in the DMARD arm will initially receive weekly oral methotrexate (MTX), co-prescribed with folic acid.

MTX will be started at 15mg weekly; this can be reduced to 10mg weekly if the higher dose is not tolerated.

If 10mg weekly MTX is not tolerated, or if MTX is ineffective, MTX may be switched to leflunomide (LEF) starting at 10mg daily. The starting dose will be increased to 20mg daily if tolerated, or reduced to 10mg every 2 days if not tolerated. The minimum LEF dose will be 10mg twice weekly. If this minimal LEF dose is not tolerated, DMARD will be stopped.

MTX will be co-prescribed with folic acid according to local practice; the folic acid dose will be at least 5mg weekly, and may be prescribed up to six days per week (folic acid is not generally given on the same day as MTX).

7.4 PARTICIPANT FOLLOW-UP SCHEDULE

7.4.1 follow-up visits

In-person follow-up assessments with the research team will be scheduled at 24 weeks post randomisation and 80 weeks post randomisation for all participants from both arms. In addition, site research teams will conduct telephone assessments with participants from both arms at weeks 4, 8, 12, 36, 48, 60 and 72.

7.4.2 Questionnaires

Throughout the trial, participants will be asked to complete questionnaires, which will be returned to either by post or electronically.

Every 4 weeks, participants will be sent a questionnaire relating to their current steroid dose, steroid dosing over each of the preceding 4 weeks, and whether the steroid dose had to be increased due to worsening of PMR symptoms.

In addition, every 12 weeks they will be asked to complete a more extensive questionnaire pack relating to their PMR and treatment-related symptoms, health-related quality of life and healthcare resource use. The questionnaires to be included in these packs are listed in section 14.10

7.4.3 DMARD monitoring blood tests (if taking DMARD)

Participants receiving DMARD therapy will require DMARD monitoring blood tests according to local guidelines. The British Society for Rheumatology guideline for DMARD monitoring suggests full 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 (32).

7.5 INTERACTION BETWEEN PRIMARY AND SECONDARY CARE

As in all instances where multiple medical teams are involved in care of a participant, accurate, concise and relevant interprofessional communication is required to ensure participants safety. Appropriate modes of communication, such as letter, telephone, email, fax, or electronic portals such as Advice and Guidance, will be utilised as necessary, depending on the degree of clinical urgency. This will be referred to as “in a timely fashion”.

GP practices who participate via sending their participants information about the study will continue to provide usual care for participants with PMR including ongoing management of relevant co-morbidities including diabetes, hypertension, osteoporosis and depression, including onward referral if necessary. If any clinical information salient to the management of such co-morbidities comes to the attention of the PI during the trial, the PI will inform the GP as appropriate.

7.5.1 DMARD monitoring blood tests in the community

Participants may for reasons of convenience choose to visit their GP practice or a local pathology centre to have blood drawn for blood tests that have been requested by research team. If so, these blood draws may be arranged directly by the participant in the same way that happens in usual care when a specialist team has requested blood tests. The site research team will remain responsible for issuing the blood test requests, and for ensuring results are checked and acted upon.

7.5.2 Potential for drug interactions

The PI will be responsible for prescribing DMARD. At the time the DMARD is initiated, the PI will check for relevant interactions of the DMARD with any concomitant medications. They will also communicate any starting or stopping of DMARD with the participants GP in a timely fashion.

DMARD should normally be paused (temporarily stopped) during a course of antibiotics that might be prescribed for intercurrent infection. For mild, uncomplicated infections in the community that have resolved by the end of

the course of antibiotics, and where broad-spectrum antibiotics have not been used, DMARD can generally be restarted after the antibiotics have finished. However, if there is any doubt, the participant and/or GP may contact the site for advice on when to restart the DMARD after completion of the course of antibiotics, depending on the infection type or severity, or if there are any other queries in relation to intercurrent infection.

MTX may accumulate in renal impairment. If acute deterioration in renal function occurs in a participant being prescribed MTX during the study, and the participant is in the community, GPs are asked via the trial specific GP letter to notify the site of this so that the MTX can be stopped, paused or dose-reduced by the site as necessary. If the participant is admitted to hospital then the admitting team will be at liberty to manage MTX dosing as clinically indicated in consultation with the rheumatology team.

7.6 INTERNAL PILOT

A 12-month internal feasibility phase will determine the likelihood of achieving i) opening of centres, ii) planned recruitment rate, and iii) achieving the recruitment target of 200 participants (41). An internal review will also be conducted after 8 months, corresponding to one-third of the total recruitment phase (42). At the end of the internal pilot phase, if Amend (amber) criteria are met, then a recovery plan detailing remedial actions will be submitted to the funder. If this is approved, the trial will proceed with caution.

8 ELIGIBILITY

Eligibility waivers to inclusion and exclusion criteria are not permitted.

8.1 INCLUSION CRITERIA FOR RANDOMISATION

Participants meeting ALL the following criteria will be considered for enrolment into the study

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.
   (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: **2 points.**
   - Previous aching of hip area (groin, buttock, lateral hip or upper thigh) in association with other features of PMR:**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).

5. At least one previous relapse during steroid therapy, defined as steroid-responsive recurrence of PMR symptoms (aching in hip and/or shoulder areas).
6. Consent to participate.

8.2 EXCLUSION CRITERIA FOR RANDOMISATION:

Participants 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 (Appendix 2) whilst receiving treatment (either methotrexate or leflunomide)
   Women of child-bearing potential (WCBP) or men unwilling to use an effective birth control measure (Appendix 2) 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) in the opinion of the local investigator.
6. Rheumatoid arthritis, psoriatic arthritis or spondyloarthritis (previous or current) in the opinion of the local investigator
7. At the baseline visit active infection of sufficient severity to be a contra-indication to commencing methotrexate, in the opinion of the local investigator.
8. Participant taking concurrent trimethoprim-sulfamethoxazole at the time of the baseline assessments
9. Active gastric ulcer at the baseline visit in the opinion of the local investigator
10. Known prior history of a significant immunodeficiency syndrome, defined as an immunodeficiency severe enough to cause recurrent infections of frequency or severity that in the opinion of the investigator would preclude DMARD treatment
11. Known prior history of hereditary galactose intolerance, hereditary total lactase deficiency or hereditary disorder of glucose-galactose malabsorption
12. Current treatment with folate antagonists including trimethoprim-sulfamethoxazole
13. Other medical condition that in the opinion of the local investigator is severe enough to seriously compromise evaluation of the primary or key secondary endpoints
14. Treatment with any immunosuppressive therapy (conventional synthetic, targeted synthetic or biological DMARD) within 3 months prior to randomisation.
15. Treatment with any investigational drug in the last 4 months prior to the start of protocol treatment.
16. Unable to complete essential study procedures and communicate with study staff independently.
17. 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

18. 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, in the opinion of the local investigator.

[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

[2] Contraindication to MTX includes comorbidities such as severe respiratory disease or chronic infections (32): investigators must use their clinical judgement, based on local practice and/or national clinical practice guidelines for methotrexate prescribing in rheumatology contexts.

9 PARTCIPANT IDENTIFICATION PROCESS

9.2 PARTICIPANT IDENTIFICATION

Potential participants may be identified through a variety of methods.

9.2.1 Participant Identification and Invitation - GP practices / Community engagement

9.2.1.1 Identification via database screening

GP practices will be contact to inform them of the current study. potentially eligible adult participants aged ≥18 years with a prior diagnosis of PMR. These individuals will be contacted by letter, issued from the GP practice, informing them about the trial and inviting them to take part. Community engagement information session will be run at each of the study sites or through local associations, whereby information on the study will be disseminated.

The invitation will include a Participant Trial Summary and the contact details for the relevant site research team. Participants who are interested in taking part in the trial will be invited to contact the team directly for further information about the study.

The postal invitation will also include a reply slip and a pre-paid envelope for the participant to return the slip to the research team. The reply slip includes a section for the potential participant to agree to be contacted about the study and requests their home telephone number, mobile telephone number, postal address and/or email address.

9.2.1.2 Identification via opportunistic screening

Posters and leaflets may also be displayed in waiting rooms and the trial will be advertised on STERLING – PMR UK website, with a link to an Australian version of the site for participants to contact a local site.

9.2.2 Participant Identification and Invitation – Secondary Care

Participants with PMR who are already under the care of a clinical team at the same site may also be invited to participate

9.2.2.1 Identification via Participant records/database review and Invitation

Participants with PMR who are already under the care of a PI may be identified via review of participant lists or databases held by their clinicians or rheumatology departments. They may be contacted by phone, post or email to introduce the trial.

Where participants are approached by post or email, they the Invitation Pack will include the telephone contact details and/or an email address of the site research team, enabling them to initiate contact themselves. They will also be provided with a Participant Trial Summary and reply slip as participant, which they can return to the research team to request further information.

9.2.2.2 Identification and Invitation during Routine Clinical Appointment

A member of a clinical care team may mention the trial to a participant during their routine care, for example, during a face-to-face or remote consultation. Where the participant expresses an interest in the study this will be followed up by a member of the research team.

9.2.3 Participant Self-Referral

Trial Advertising

Posters and leaflets may also be displayed in community areas such as pharmacies and hospital Outpatient areas; these will direct the participant to their local site and the STERLING-PMR website. Promotional material may also be issued to relevant local, regional or national participant support groups such as Arthritis SA and Arthritis WA to send out via their mailing list or advertise on their website, internet forum, Facebook, Twitter or other social media. This will direct participants to the STERLING-PMR website.

The STERLING-PMR website will contain the participant information documentation for the study and contact details for the sites, in addition to other ethically approved information. Participants will then be able to contact the research team to initiate discussions about the study and the screening suitability process (see section 9.3).

Eligibility screening and recruitment to the study will take place in appropriate locations, such as rheumatology clinics, day units, clinical research facilities or other suitable locations at the site.

9.3 SCREENING-SUITABILITY PHONE CALL

Research nurses or clinical trial coordinator from each participating site will contact potential participants to arrange a phone call to assess their suitability for screening (Pre screening). Alternatively, the phone call may be initiated by participants contacting the site directly.

During the Pre screening phone call the research nurse/ clinical trial coordinator will provide further information about the trial and obtain verbal consent to conduct an assessment of the participant's suitability for screening, supported by a checklist based upon the trial eligibility criteria, participant's co-morbidities and any medications the participant is already using.

If the participant prefers not to use the telephone, for example if they have difficulties listening, speaking or prefer a family member or carer to be present, the screening-suitability activity may be conducted face to face at the research site, either as a scheduled study appointment or at a time when they are attending for their usual clinical care, and may be combined with part of the screening visit if circumstances allow.

9.4 ELIGIBILITY SCREENING

Following the pre-screening- call, if the participant is considered potentially suitable for the study, they will be invited to attend a further in-person (face to face) screening assessment.

The site research team will require further medical information about the participant from their medical notes to support the eligibility screening visit process (e.g. co-morbidities, medication history, and historic ESR/CRP results). Depending upon participant data sharing arrangements between the site and the GP practice it may be possible for the notes to be reviewed directly by the research team. However, where data sharing arrangements do not facilitate this the team will request the information from their GP. Agreement for this data collection can be obtained from the participant by email or verbally during the screening suitability process. The consent discussions and participant agreement must be adequately documented in the participant notes.

Prior to the in-person screening visit participants will be posted or emailed the full Participant Information Sheet and Full Informed Consent Form to allow them time to read these before attending the visit.

10 INFORMED CONSENT

The PI at the site retains overall responsibility for the informed consent of participants at their site and must ensure that any person who is delegated responsibility to participate in the informed consent process is duly authorised, trained, and competent to participate, according to the ethically approved protocol, principles of Good Clinical Practice (GCP), and Declaration of Helsinki 1996.

Where a test has already been performed as part of clinical care, and is within the required timeframe, it does not need to be repeated, but cannot be used for trial purposes until the participant has given verbal consent for this.

At the in-person screening visit the Investigator and/or other relevant members of the site research team will provide the participant with full and adequate verbal information about the study to complement the Participant Information Sheet and the information given during the screening suitability phone call. This will include the background, purpose, and the risks/benefits of participation. They will ensure each participant is given the opportunity to ask questions.

For scientific validity of this open-label study it is important that participants only enter the trial if they understand and would be prepared to follow the treatment strategy chosen for them by the randomisation process. To this end, potential participants will also be provided with the same written information (consumer medicines information sheet) about methotrexate that would be provided to any participant initiating methotrexate in routine care. At all times, the written information provided will reflect the latest current information about methotrexate/DMARD.

Participants will have as long as they need to consider participation and will be given the opportunity to discuss the study with their family and other healthcare professionals. Assenting participants will then be invited to provide informed written consent and undergo formal assessment of their eligibility (screening). No clinical tests or assessments required specifically for the purposes of the study will be undertaken until written informed consent has been provided by the participant.

A record of the consent process, detailing the date of consent and those involved in the consent process, will be added to the participant's hospital notes. The original copy of the signed and dated informed consent form will be stored in the Investigator Site File. A copy is also filed in the participant's hospital notes (as per local practice), one given to the participant, one provided to the GP.

The right of a participant to refuse consent without giving reasons will be respected.

The participant must remain free to withdraw at any time from the study without giving reasons and without prejudicing their further treatment. The participant will be provided with a contact point where they may obtain further information about the trial. Where a participant is required to re-consent, or new information is required to be provided to a participant, it will be the responsibility of the site research team to ensure this is done in a timely manner.

Site staff are responsible for:

- Checking that the correct (current approved) version of the PIS and Consent Form(s) is/are used
- Checking that information on the Consent Form(s) is/are complete and legible
- Checking that the participant has completed/initialled all relevant sections and signed and dated the form(s)
- Checking that an appropriate member of staff has countersigned and dated the Consent Form(s) to confirm that they provided information to the participant
- Checking that an appropriate member of staff has made dated entries in the participant's medical notes relating to the informed consent process (i.e. date information given, consent signed, those present)
- Making sufficient copies and filing the original consent form(s) in the investigator site file, and filing a copy in the participant's medical notes.
- Giving the participant a copy of their signed PIS/Consent Form(s) and a STERLING Trial Summary Sheet.

10.1 LOSS OF CAPACITY FOLLOWING INFORMED CONSENT

Where valid informed consent is obtained from the participant and the participant subsequently becomes unable to provide ongoing informed consent by virtue of physical or mental incapacity, the consent previously given when capable remains legally valid.

Participants who lose capacity after informed consent has been obtained will continue with protocol treatment and assessments in consultation with the site Principal Investigator and the participant's carer / family with the participant's best interests foremost in the decision-making process. Ongoing collection of safety and follow-up

data will continue via the clinical care team for inclusion in the trial analysis in order to preserve the integrity of the trial's intention to treat analysis and to fulfil regulatory requirements specifically for pharmacovigilance purposes.

10.2 COLLECTION AND USE OF FULL PARTICIPANT NAME

Full participant name will be present on Informed Consent Documents and Contact Details Forms (required in order to send participant the trial questionnaires). This information will be stored securely at the trial site separate to all other STERLING-PMR trial data.

Full participant name will also be required on the reply slip that potential participants may return to the site in order to arrange the screening-suitability discussion.

11 REGISTRATION AND RANDOMISATION

Recruitment into the study is classed as a two-step process involving an initial registration of all potential participants, followed by randomisation for eligible participants.

11.1 REGISTRATION

Following confirmation of written informed consent, participants will be registered into the trial as soon as possible by an authorised member of the site research staff, as detailed on the Authorised Personnel Log. Informed consent for entry into the trial must be obtained prior to registration. Registration will be performed centrally using the automated web-based registration and randomisation system.

The person registering the participant must have the following information available at the time of accessing registration system:

- Personal authorisation codes and PIN;
- Name of study research site and site code;
- Participant details, including initials, biological sex, date of birth
- Confirmation of written informed consent, and date

All participants will be allocated a unique trial identification number after they have been registered.

Web address for 24-hour randomisation: https://lictr.leeds.ac.uk/webrand/

After trial registration the site research team will:

- Record the participant details on the STERLING Participant ID Log in the Investigator Site File
- Add the unique participant ID number to all CRFs
- Return an electronic copy of the completed consent form to CTRU via secure file transfer
- Ensure that participants are notified of their next appointment dates (e.g. chest x-ray, baseline assessment).

Following registration, CTRU will send an automated email to the site research team to confirm that a participant has been registered. This is to be checked by the participating site to ensure the information is correct.

11.2 CONFIRMATION OF ELIGIBILITY

After the participant has provided written informed consent and prior to the baseline assessments each participant will be assessed for their suitability for treatment. Please see Section 14.4 for details.

A maximum of 6 weeks will be permitted between registration and randomisation. During this time participants will continue with standard of care treatment.

11.3 RANDOMISATION

Randomisation will be a 1:1 allocation ratio to receive either Usual Care (steroid taper) Alone or Usual Care plus DMARD. Randomisation will be based on a minimisation algorithm with random component to ensure treatment groups are well-balanced for the following participant characteristics:

- site;
- number of previous relapses
- biological sex;
- prednisolone dose equivalent prior to last relapse (5mg or less, greater than 5mg) (see Appendix X for details of conversions from other glucocorticoids).

Randomisation process and timing

Participants who have previously been registered and have confirmation of eligibility will be randomised into the trial by an authorised member of the site research staff, as detailed on the Authorised Personnel Log. Randomisation will be performed centrally using the same CTRU automated web-based system as was used during registration and the same site code, authorisation code and PIN will be required. The baseline assessments and questionnaires should be completed BEFORE the participant is randomised.

The following information will be required whilst accessing the automated web-based system:

- site
- number of previous relapses
- biological sex
- prednisolone dose equivalent prior to last relapse (5mg or less, greater than 5mg)
- confirmation of participant's eligibility for the trial
- confirmation of informed consent
- confirmation of completion of baseline participant questionnaires

Web address for 24-hour randomisation: https://lictr.leeds.ac.uk/webrand/

Once randomisation is complete, the system will allocate a treatment arm for the participant and inform the user of the allocation.

The CTRU will send an automated email confirming participant randomisation and confirming the treatment allocation to the:

- site research team and
- site pharmacy

Site Research Team Post-Randomisation Activities

- Check automated email from CTRU to ensure participant information is correct e.g. initials, date of birth
- Update the participant's record on the STERLING Participant ID Log by adding details of the treatment allocation
- Return a copy of the completed participant contact details forms to CTRU
- Provide the participant with a Trial ID card and inform them that it should be carried at all times and presented to medical staff should they be admitted to hospital during their time in the trial or should they visit their GP. They will also discuss with the participant the situations in which it would be most appropriate to seek support from the site research team and the situations where it is more appropriate to approach their GP for advice.
- Notify the participant's GP of their participation in the trial using the appropriate approved STERLING GP Letter.
- Actions specific to participants randomised to receive Usual Care plus DMARD:
    - Agree with the participant what day of the week their will take their methotrexate. Prescribe an initial 6-week supply of methotrexate with folic acid following local procedures. It is the PIs responsibility to ensure that participants are counselled about the importance of how and when to take their methotrexate and folic acid. To ensure that participants receive up to date counselling and the same safety procedures as participants in routine care, participants will be provided with written participant information materials that would be provided for participants starting a DMARD in routine care, for example booklets produced by the independent charity Versus Arthritis, to supplement the verbal information given.
    - Issue paper DMARD monitoring blood tests laboratory request forms for the duration of the initial methotrexate prescription, with clear instructions for the participant about the time windows during which each test must be done, and the options they have for the blood draw (e.g. by appointment with their GP practice, or by visiting the site by appointment or drop-in, or a local pathology clinic according to local procedures). The participant will need to arrange their own blood tests.
    - Specifically remind the participant that if they develop an intercurrent infection they may need to stop their DMARD (but continue steroid) and inform the hospital team for advice on when the DMARD can be re-started.

Site Pharmacy Team Post-randomisation Activities:

- Record the participant details on the STERLING Participant ID Log in the Investigator Site File, including treatment allocation (applies to participants from both arms).

- Participants randomised to receive Usual Care plus DMARD:
    - Dispense prescribed supply of methotrexate and folic acid.
    - Apply trial specific labels to packaging of methotrexate
    - Check the participant's (and/or carers', if relevant) understanding about how and when to take methotrexate. Check that they are aware that methotrexate is a WEEKLY medication.

12 TRIAL MEDICINAL PRODUCT MANAGEMENT

12.1 Pharmacy Registration and Set-Up

A designated Pharmacist who takes overall responsibility for all pharmacy aspects of the trial must be identified and will be assigned as the Lead Pharmacist. This person will be listed on the main site Authorised Personnel Log and must sign the Lead Pharmacist Declaration. CTRU will provide participating pharmacies with a Pharmacy Site File (PSF). All STERLING trial related documentation must be retained in the PSF (or a file note documenting its location). When all approvals and essential documents are in place CTRU will formally notify the site and pharmacy that potential trial participants can be approached.

12.2 Investigational Medicinal Product (IMP) Definition

Within the trial, the following are classed as IMPs:

- methotrexate
- leflunomide

12.3 IMP Composition

Methotrexate

Composition: Oral tablets containing 2.5 mg methotrexate (AUS Variation: or 10mg of methotrexate)

Leflunomide

Composition: Oral tablets containing either 10mg or 20mg of leflunomide

12.4 IMP Supply

Both methotrexate and leflunomide are licensed in the UK and generic 'off the shelf' site supplies will be used. There is no requirement to ring-fence either methotrexate or leflunomide for the STERLING trial.

12.5 IMP Storage and Handling

For details on storage and handling please refer to the most recent version of the specific manufacturer's SmPC for both IMPs. Copies of these should be maintained in the Investigator Site File and Pharmacy Site File at the site.

Trial specific SPCs for both IMPs will also be provided in the Investigator Site File and Pharmacy Site File Investigator Site File and Pharmacy Site File at the site and should be used for pharmacovigilance purposes.

12.6 IMP Prescribing

Prescribing of DMARD and prednisolone taper be the responsibility of the site rheumatologist. Results of the most recent available blood monitoring tests must be checked before each new prescription of MTX and continuation of the taper schedule is issued and found to be acceptable relative to the parameters listed in section 13.4.1.

The prescriber should specify the day of intake on the prescription. Prescriptions will be sent to the local site pharmacy for dispensing. As the IMPs are generic hospital stocks being prescribed 'off-label' no trial-specific prescription is required. sites will use their local standard prescriptions. A note of the location of completed prescriptions should be stored in the Pharmacy Site File.

Where the site uses electronic prescribing programmes the pharmacy must provide verification that checks of the prescribing programmes have been made to ensure that the regimen is correct and authorised by the investigator or delegate.

12.7 IMP Labelling

As the IMPs are marketed within the UK but will be used outside their marketing authorisation additional labelling in line with Directive 2001/20/EC and the Medicines for Human Use (Clinical Trials) Regulations 2004 (amended 2006) will be applied. The labelling will include the following:

- 'For clinical trial use only'
- Trial Name: STERLING trial
- EudraCT number: 2023-000130-15
- Participant Trial ID

site pharmacies will be responsible for applying the labels to both MTX and LEF.

Participants will be issued with a Trial ID card by the rheumatology team at the time of STERLING trial randomisation. This will detail:

- The name of the trial
- Participant name
- Participant trial number
- the Investigator name and telephone numbers to contact in a medical emergency
- Sponsor name and contact details
- IMP allocation (a new card will be issued for participants who transfer from MTX to LEF)
- A request to notify the research team if the participant is admitted to hospital in order to monitor SAEs fulfilling this definition

12.8 IMP Dispensing

Where the participant is randomised to the Usual Care plus DMARD arm, the site pharmacy will receive a STERLING trial Participant Randomisation notification following randomisation. The participant ID log must be updated accordingly.

Upon receipt of the prescription from the rheumatology team, the site pharmacy will then be responsible for dispensing an initial 6-week supply of MTX and folic acid directly to the participant at the end of their baseline appointment. This should ensure the participant has adequate supplies until the next supply.

Subsequent supplies will be posted to participants at home by the site pharmacy. In order to avoid issuing excessive supplies of MTX it is advised that the second dispensing should contain a 2-month supply of MTX, and subsequent dispensing contain 3 months' worth of MTX. However, amounts can be varied in accordance with the participants' requirements e.g. should a participant be planning a holiday and requires that adequate amounts are dispensed to cover this period.

A copy of any trial specific dispensing instructions must be retained in the relevant section of the PSF (or a statement of its location) and should be available upon request. Sites are responsible for the development and accuracy of any additional process documents that they produce.

Sites will issue trial participants allocated to the DMARD arm with 2.5mg tablets of MTX and not 10mg tablets.

12.9 IMP Accountability

No trial-specific accountability logs are required. Dispensing records will be in line with local standard practice and as a minimum will ensure that IMP is fully traceable by batch number.

Treatment compliance is recorded by the Research Nurse on the Case Report Form; there is no requirement for compliance checks or routine monitoring to be performed within pharmacy.

The trial pharmacist will sign a document to confirm that local hospital systems are in place to cover drug ordering, drug receipt, drug storage and dispensing, and will enable accurate traceability of all drugs used in the trial.

Unused, used or partially used stocks of IMP should be disposed of at site according to local policy.

12.10 Non-IMPs

Within the trial, the following are classed as Non-Investigational Medicinal Product (NIMPs):

- **Folic acid (FA)**

Composition: Oral tablets containing 5mg of folic acid, usually prescribed at the same time as prescribing MTX. It is not necessary to prescribe folic acid alongside LEF. Generic 'off the shelf' site supplies will be used. There is no requirement to ring-fence folic acid for the STERLING trial.

13 TREATMENT

Participants enter the trial already receiving usual care (steroid therapy). Treatment prior to randomisation is not considered part of this clinical trial.

Following randomisation treatment within the trial is:

- **Arm A (Usual Care):** Those randomised to usual care alone continue to receive usual care, anticipated to include steroid therapy.

or

- **Arm B (Usual Care plus DMARD):** Those randomised to usual care plus DMARD continue to receive usual care, anticipated to include steroid therapy.. In addition, they will commence **weekly** oral MTX therapy under the management of the rheumatology team. Folic acid is also prescribed at the same time as oral MTX.

  If MTX is not tolerated this may be switched to the second-line DMARD, LEF (see section 13.2).

13.1 METHOTREXATE (MTX) REGIMEN

13.1.1 Methotrexate Pre-treatment Investigations

During screening participants will have undergone a number of assessments in order to assess their suitability/fitness to receive MTX. Please see section 14.4 for details.

13.1.2 Ongoing Blood monitoring during methotrexate therapy

Blood monitoring of methotrexate will follow local recommendations. As a guide the British Society for Rheumatology DMARD monitoring guidelines recommend FBC, U+E and LFT approximately 8ml taken each draw:

- every two weeks until on stable dose for six weeks
- then monthly for three months and
- quarterly thereafter

The site team will issue sufficient laboratory request forms to cover the duration of each prescription and will check the results of the monitoring blood tests before each new prescription of MTX is issued. Providing the results of the prior test do not fall within the limits referred to in section 13.4.1 and are acceptable according to local physician discretion, windows either side of these blood monitoring dates will be allowed. Please see Schedule of Events for details of appropriate windows.

13.1.3 Rules for concomitant therapy in participants receiving methotrexate

All treatments being taken by the participants on entry to the trial or at any time during the trial in addition to the investigational medicinal product are regarded as concomitant treatments and must be documented in the participant's hospital notes; only concomitant treatments relevant to this trial will be recorded on the eCRF as required.

Concomitant medications felt to be clinically indicated would be allowed during the study so long as they do not interfere with the investigational medicinal products (please refer to the applicable SmPC/IB).

Many drug interactions noted in SmPCs relate principally to high-dose MTX, rather than the low-dose MTX used in STERLING and in standard rheumatology practice. Clinicians should review the current DMARD being prescribed and use clinical judgement when initiating any new therapies known to interact with MTX, taking into account whether the interaction is clinically significant for MTX at the dose being used.

13.1.4 Use of Folic Acid during MTX therapy

The administration of folic acid appears to ameliorate side-effects of MTX. Therefore, trial participants prescribed oral weekly MTX must be also prescribed 5mg folic acid at least once per week but up to six days per week. This must **not** be taken on the same day of the week that MTX is taken.

The dose of folic acid remains the same (5mg up to six days per week) for participants receiving MTX, regardless of the MTX dose.

13.1.5 Use of antibiotics during MTX therapy

MTX should never be co-administered with trimethoprim-sulfamethoxazole due (also both folate antagonists) to cytopenia risk.

MTX may be given alongside long-term antibiotics (except trimethoprim-sulfamethoxazole) in some situations, for example long-term prophylactic antibiotics. The site will include a request in the GP letter requesting that should the GP initiate a long-term course of antibiotics the site investigator should be informed in writing.

In the event of an acute infection requiring antibiotic therapy MTX may need to be omitted until the infection has resolved and the antibiotics have stopped. Please see Section on MTX Delays and Dose Modifications below for further detail (section 13.1.16)

Participants will be advised to provide any clinician with their Participant ID card to inform them that they are participating in the study which will advise that they are taking a DMARD. The card will also instruct participants to contact the site research team if they are prescribed antibiotics so appropriate advice can be given.

13.1.6 Vaccinations during MTX therapy

Live vaccines, such as the vaccine for yellow fever, are contra-indicated in people taking oral MTX. There is no contra-indication to receiving mRNA vaccines, including currently available vaccinations against SARS-CoV-2.

Current national guidance in regard to vaccinations during MTX therapy must be followed. At the time of preparation of this protocol (October 2022), the British Society for Rheumatology states on its website: “In response to the VROOM study (44), adult rheumatology participants, who are stable on methotrexate, may consider stopping methotrexate after booster vaccination for COVID-19 for 2 weeks (skipping 2 doses of methotrexate). There is no need to stop prior to vaccination. There is a small risk of flare. This has been shown to improve vaccine response to COVID-19.” (45)

13.1.7 Use of Proton-Pump Inhibitors during MTX therapy

Proton pump inhibitors may be prescribed alongside low-dose MTX if clinically indicated.

13.1.8 Use of other Experimental Drugs during MTX therapy

Use of any other experimental drug during MTX therapy is not permitted.

13.1.9 Methotrexate Dosing and Frequency

For the treatment of rheumatic conditions oral MTX must be prescribed **weekly** (low-dose). Daily MTX administration would be classed as high-dose and carries a high risk of toxicity

The STERLING trial specifies a Starting Dose, Target Dose and Minimal Dose for MTX. Due to inter-individual variation in oral MTX bioavailability and toxicity, dose titration is used to achieve a maximum tolerated dose of MTX for each participant, which will be between 7.5mg weekly and 25mg weekly.

The participant's GP should be informed in writing of all dose escalations, reductions and other modifications and should be requested to update this dose information on the participant's healthcare record.

The Starting Dose, Target Dose and Minimal Dose are specified in Table 1.

In the following discussions, "frailty" is not specifically defined and will be assessed at the physician's discretion on clinical grounds, taking into account all relevant circumstances. For example, some participants with multiple long-term conditions sufficient to cause significant limitations of daily activities or frequent falls might be deemed as clinically frail.

Methotrexate Dosing:	Dose, reason
Starting Dose	15mg weekly for most participants 10mg weekly in frailty (physician's discretion) or renal disease i.e. stage 3 chronic kidney disease defined as eGFR <60mg/ml (value provided by local laboratory)
Target Dose (if tolerated)	25mg weekly is the maximum permitted Recommend 15mg weekly for participants with renal disease i.e. stage 3 chronic kidney disease defined as eGFR <60mg/ml (value provided by local laboratory)
Minimal Dose	7.5mg weekly If this is not tolerated, stop MTX and folic acid, consider starting LEF
Maximum Tolerated Dose	Established for each individual by dose titration; must not exceed 25mg weekly.

Table 1.

13.1.10 Methotrexate Starting Dose

The Starting Dose of MTX will generally be 15mg weekly. This may be reduced to 10mg weekly at the physician's discretion for individuals with relevant co-morbidities e.g. frailty or significant renal disease i.e. stage 3 chronic kidney disease defined as eGFR < 60mg/ml.

Participants may wish to delay their first MTX dose for up to two weeks after the baseline visit.

Participants will remain on the Starting Dose until at least the week 4 follow-up telephone consultation with the site team.

13.1.11 Methotrexate Target Dose

The earliest timepoint for potential dose escalation will be following the week 4 telephone assessment, but may occur following any of the telephone assessments up to the week 26 clinical assessment.

Dose escalation should only be performed once the latest DMARD monitoring blood tests (see section 13.1.2) have been checked to assess for any biochemical/haematological abnormalities (see section 13.4.1) and where the participant is not experiencing other intolerable toxicities e.g. nausea.

If DMARD monitoring is satisfactory (see section 13.4.1), participants should be advised to increase their MTX dose in line with their Target Dose. The Target Dose is 25mg weekly for most participants, but prescribers should consider reducing the Target Dose to 20mg weekly for participants with renal dysfunction or frailty.

13.1.12 Methotrexate Minimal Dose

The Minimal Dose of MTX will be 7.5mg weekly. If this is not tolerated, the MTX and folic acid will be stopped, with the option to commence LEF therapy.

13.1.13 Methotrexate Split-Dosing

Taking the prescribed dose of MTX generally requires the participant to take multiple tablets to achieve the dose required. These tablets can be taken either together or split over the day. Splitting the dose of oral MTX may improve bioavailability (46). Morning or evening administration is equally acceptable; some participants find morning administration more convenient, while other participants report that side-effects are less troublesome if MTX is taken in the evening. However, split-dosing, if undertaken, should be restricted to a single day of the week. MTX should *not* be taken on more than one day in a given week due to toxicity risk.

13.1.14 Duration of Treatment

The anticipated duration of MTX treatment will be 18 months from the baseline visit, but can be stopped at any time in the event of toxicity or from 3 months at Maximal Tolerated Dose in the event of inefficacy. After MTX has been stopped, the participant will commence LEF, unless contra-indicated.

13.1.15 MTX compliance

Where possible within the conduct of this trial, local systems and processes to reduce the risk of MTX dosing errors should be followed. For example, participants must be instructed on the importance of adhering to the once-weekly dosing. Therefore, when initiating MTX, it is usually recommended to discuss and agree with the participant a specified day of the week that they will take their MTX. Where the participant is supported in the management of their condition by a family member of carer, with the consent of the participant the family member or carer must also be involved in these discussions.

Participants will be advised to maintain a record of their DMARD doses in addition to their steroid doses and provided with a personal diary for this if required. Details of DMARD compliance will be collected by the site research team during telephone and face-to-face assessments.

13.1.16 MTX Delays and Dose Modifications

MTX is a weekly medication; side-effects tend to be most noticeable in the 24-28 hours after taking each dose. For this reason, participants may wish to delay their first MTX dose for up to two weeks after the baseline visit. Scheduled dates and windows of blood monitoring tests should be scheduled in accordance with the date MTX is commenced rather than with the baseline visit.

Participants may immediately reduce their MTX dose in the event of toxicity or side-effects but should contact their rheumatologist as soon as possible to discuss other appropriate management.

Please also see section 13.4.1 regarding Laboratory Abnormalities and Infections.

13.1.17 Antibiotic Use

In the event of an acute infection requiring antibiotic therapy, MTX should be omitted until after the course of antibiotics has ended and the participant has recovered from their infection. Participants should contact the site as to when they should resume taking MTX; they may be advised to re-start it initially at a lower dose and then re-escalate to maximum tolerated dose. The reason for starting at a lower dose is that the gut microbiome is involved in methotrexate metabolism and may be disturbed by some broad-spectrum antibiotics.

13.1.18 Renal Impairment

Methotrexate is excreted via the kidneys and MTX dosing should be reviewed in the event of acute renal impairment.

13.1.19 Most frequently anticipated toxicities of MTX

In a systematic literature review (47), the pooled prevalence of adverse effects was 80.1% in RCTs of MTX, and 23% in observational studies. In RCTs 6.7% discontinued MTX due to adverse effects, whereas in observational studies 15.5% discontinued due to adverse effects.

Commonly reported side-effects of methotrexate include nausea (19.2% in RCTs), altered taste, abdominal pain or discomfort (9.3% in RCTs), diarrhoea (8.0% in RCTs), headache (8.5% in RCTs), dizziness (7.2% in RCTs), fatigue, and thinning of the hair (6.9% in RCTs) and mouth ulcer or soreness (7.8% in RCTs). These are often easily noticed by the participant because of the weekly administration. In this trial, these well-known adverse effects of MTX are not necessarily considered “toxicities” unless they are troublesome to the participant. Folic acid, 5mg up to six days per week, may help to alleviate many of these common side-effects. Management advice may also include review of diet, smoking cessation, mouthwashes for sore mouth or simple analgesia for headache, at the clinician’s discretion. An extra cup of strong coffee, or dark chocolate, the morning after MTX administration is sometimes recommended on the basis that caffeine antagonises adenosine signalling in the central nervous system and might alleviate the central nervous system side-effects of MTX (48).

MTX may cause mild cytopenia including neutropenia. Neutrophil counts below 1x10^9/L, if persistent on rechecking, would be an indication to stop MTX. Pancytopenia is rare and usually only seen in MTX overdose.

MTX-related pneumonitis is an idiosyncratic reaction and is very rare (47): it was reported in <0.1% of participants in RCTs.

Abnormalities of liver function tests including AST/ALT are frequently observed in patients receiving MTX; in the meta-analysis (47)the pooled prevalence of any elevated liver enzyme was 15.3% in 6 RCTs. The concern is that MTX may have a profibrotic effect; it is contra-indicated in participants who already have liver cirrhosis. A study of liver stiffness using Fibroscan (49) in participants receiving MTX showed no correlation with cumulative MTX exposure but significant correlations with markers of obesity (body mass index, waist circumference).

Blood monitoring tests during MTX treatment commonly show a minor rise in the mean cell volume (mcv). This is benign and is due to the polyglutamation of MTX inside erythrocytes. In rheumatoid arthritis, a rise in mcv during MTX treatment has been reported to be associated with better therapeutic response to MTX.

13.1.20 Methotrexate and pregnancy

MTX must not be taken in pregnancy as it is a teratogen. In line with the SmPC MTX must be stopped six months in advance of trying to conceive in both male and female participants and contraception (see appendix 2) must be used for this period. In the case of male participants, the contraceptive measures can be taken by either themselves or their female partners. In the event of unplanned pregnancy MTX must be stopped immediately.

13.2 SWITCHING TO LEFLUNOMIDE

The beneficial effects of MTX in rheumatic diseases are generally quoted as taking at least 3 months to accrue. If MTX is not tolerated therapy may be switched to the second line DMARD, LEF.

13.2.1 Site Research Team Activities Upon Transfer to LEF

- Update the participant's record on the STERLING Participant ID Log by adding details of the treatment allocation.
- Notify the participant's GP of their transfer to LEF.
- Discuss with the participant the situations in which it would be most appropriate to seek support from the site research team and the situations where it is more appropriate to approach their GP for advice.
- Provide the participant with a Blood Pressure monitoring device and explain to participants how and when (see section 13.3.4) this should be used.
- Prescribe an initial 6-week supply of leflunomide following local procedures. It is the prescriber's responsibility to ensure that participants are counselled about the importance of how and when to take their leflunomide. To ensure that participants receive up to date counselling and the same safety procedures as participants in routine care, participants will be provided with written participant information materials that would be provided for participants starting a DMARD in routine care, for example booklets produced by the independent charity Versus Arthritis, to supplement the verbal information given.
- Issue paper or electronic DMARD monitoring blood tests laboratory request forms for the duration of the initial leflunomide prescription, with clear instructions for the participant about the time windows during which each test must be done, and the options they have for the blood draw (e.g., by appointment with their GP practice, or by visiting the site by appointment or at a local pathology clinic.). The participant will need to arrange their own blood tests, except where this falls within the clinic visit schedule.

- Specifically remind the participant that if they develop an intercurrent infection they may need to stop their DMARD (but continue steroid) and inform the hospital team for advice on when the DMARD can be re-started.

13.3 LEFLUNOMIDE REGIMEN

13.3.1 MTX wash-out

MTX must be stopped before LEF is commenced (they should not be taken together in this trial).

MTX polyglutamates may be retained in tissues for some weeks after MTX cessation, and therefore a wash-out period of at least 2 weeks is recommended before starting LEF; this may be extended to 8 weeks where required.

13.3.2 LEFLUNOMIDE CONTRAINDICATIONS

Leflunomide must not be commenced if contra-indicated in the opinion of the local Investigator. This includes:

- hypersensitivity to leflunomide
- uncontrolled hypertension*
- current active infection** at the time of commencement. In this case, leflunomide treatment may be deferred and started after the infection has resolved.

***** BP higher than 145/95 measured at study visit and over 140/90 when measured at home or in the community within 6 weeks prior to the proposed commencement of leflunomide

- ****** including but not restricted to AIDS, active tuberculosis infection or other serious infection

13.3.3 Leflunomide Pre-treatment Investigations

The following investigations are required before commencing leflunomide:

- Blood pressure
- Full blood count (FBC), including differential white cell count and platelet count
- Liver function tests (LFT) including alanine aminotransferase (ALT) and albumin
- Urea and electrolytes (U+E) including estimated glomerular filtration rate (eGFR)
- Pregnancy test where participant is a woman of child-bearing potential

A chest radiograph will have been performed prior to commencing MTX therapy and therefore does not require repeating prior to commencing LEF.

Providing the above blood tests have been performed within the preceding 6 weeks and the results do not fall outside the limits referred to in section 13.4.1 and are acceptable according to local physician discretion there is no need to repeat these prior to commencing LEF.

Where the latest results are either outside acceptable parameters or have been done more than 6 weeks ago these will need repeating and found to be within acceptable parameters before commencing LEF.

13.3.4 Ongoing Blood monitoring and Blood Pressure Assessments during Leflunomide therapy

Monitoring of leflunomide via blood tests and blood pressure measurements will follow local recommendations. As a guide the British Society for Rheumatology DMARD monitoring guidelines recommend FBC, U+E, LFT and a blood pressure measurement:

- every two weeks until on stable dose for six weeks
- monthly for three months and
- quarterly thereafter

Blood Tests

The site team will issue sufficient laboratory request forms to cover the duration of each prescription and will check the results of the monitoring blood tests before each new prescription of LEF is issued.

Providing the results of the prior tests do not fall within the limits referred to in section 13.4.1 and are acceptable according to local physician discretion, windows either side of these blood monitoring dates will be allowed. Please see Schedule of Events for details of appropriate windows.

Blood Pressure

Blood pressure (BP) should be measured at the same time as each blood test. Participants who transfer onto LEF from MTX will be issued with their own blood pressure monitor. Therefore, it is acceptable for the BP to be measured either by the GP practice or self-managed by the participant. Participants will receive instruction from the research team regarding the use of the monitor and written instructions advising them that:

- should the BP value be over 140/90 then it should be rechecked on another occasion within one week. If on re-checking, it is still over 140/90, then the site research team should be notified within one further week.
- should the BP value be over 180/120 (regarded as severe hypertension), the research team should be contacted on the next working day so that appropriate clinical action can be taken.

The team will promptly communicate new or significant findings of high blood pressure to the GP, as this may require escalation of antihypertensive therapy by the GP.

13.3.5 Rules for concomitant therapy in participants receiving Leflunomide

All treatments being taken by the participants on entry to the trial or at any time during the trial in addition to the investigational medicinal product are regarded as concomitant treatments and must be documented in the participant's hospital notes; only concomitant treatments relevant to this trial will be recorded on the eCRF as required.

Concomitant medications felt to be clinically indicated would be allowed during the study so long as they do not interfere with the investigational medicinal products (please refer to the applicable SmPC/IB).

Clinicians should review the current DMARD being prescribed and use clinical judgement when initiating any new therapies known to interact with LEF.

Warfarin can interact with leflunomide. Warfarin dose may need to be adjusted alongside LEF therapy. GPs are informed of this as part of GP letter.

13.3.6 Leflunomide Dosing and Frequency

The STERLING trial specifies a Starting Dose, Target Dose and Minimal Dose for LEF. A dose titration procedure will be used establish a Maximum Tolerated Dose of LEF for each participant, which will be between 10mg twice per week and 20mg daily.

An initial three-day loading dose of LEF is suggested in the SmPC but this is rarely utilised in clinical practice in rheumatology and will not be used in this trial.

The participant's GP should be informed in writing of all dose escalations, reductions and other modifications and should be requested to update this dose information on the participant's healthcare record.

The Starting Dose, Target Dose and Minimal Dose are specified in Table 2.

Leflunomide Dosing	Dose, reason
Starting Dose	10mg daily for most participants 10mg alternate days for individuals with relevant co-morbidities e.g., frailty, at the physician's discretion
Target Dose (if tolerated)	20mg daily is the maximum permitted dose.
Minimal Dose	10mg twice per week If this is not tolerated, stop LEF.
Maximum Tolerated Dose	Established for each individual by dose titration; should not exceed 20mg daily.

Table 2

13.3.7 Leflunomide Starting Dose

The Starting Dose of LEF will generally be 10mg daily but may be reduced to 10mg alternate days for individuals with relevant co-morbidities, for example significant frailty, at the physician's discretion.

Participants will remain on this dose until at least the week 4 follow-up telephone consultation with the site team.

13.3.8 Leflunomide Target Dose

The earliest timepoint for potential dose escalation will be following the week 4 telephone assessment but may occur following any of the telephone assessments up to the week 26 clinical assessment.

Dose escalation should only be performed once the latest DMARD monitoring blood tests and blood pressure (see section 13.3.4) have been checked to assess for any biochemical/haematological abnormalities and blood pressure has been taken to exclude hypertension (value should be below 140/90).

13.3.9 Leflunomide Minimal Dose

The Minimal Dose of LEF will be 10mg twice per week. If this is not tolerated, LEF will be stopped, and participants will continue therapy with Usual Care (steroids) alone; no further DMARD will be offered (50).

13.3.10 Duration of Treatment

Participants in the DMARD arm will commence LEF only after stopping MTX. Providing it is tolerated and there is no toxicity, the LEF treatment will continue until the final study visit at 18 months.

13.3.11 Leflunomide compliance

Where possible within the conduct of this trial, local systems and processes to reduce the risk of LEF dosing errors should be followed.

Participants will be advised to maintain a record of their DMARD doses in addition to their steroid doses and provided with a diary for this if required. Details of DMARD compliance will be collected by the site research team during telephone and face-to-face assessments.

13.3.12 Leflunomide Delays and Dose Modifications

Please also see section 13.4.1 regarding Laboratory Abnormalities and Infections.

13.3.13 Most frequently anticipated toxicities of LEF

The commonest side-effect of LEF is gastrointestinal upset including abdominal pain, loose stool or diarrhoea, and less commonly nausea, vomiting, or raised liver function tests. These adverse effects are most prominent in the first two weeks of therapy and tend to improve thereafter (50). A rise in blood pressure is uncommon and can usually be managed with antihypertensive therapy. Hair thinning may occur. Cytopenia is described but is not common. LEF-associated pneumonitis is very rare. LEF toxicities may persist after stopping therapy due to the long half-life of LEF in the body. If necessary, a cholestyramine washout procedure reduces the LEF levels to very low levels (50).

13.3.14 Leflunomide and pregnancy

LEF is a teratogen and must not be taken in pregnancy. In line with the SmPC, both male and female participants must use contraception (see appendix 2) for the duration of their treatment with leflunomide. In participants who are women of child-bearing potential (WCBP) LEF must be stopped two years in advance of trying to conceive. If a waiting period of up to approximately 2 years under reliable contraception is considered unpractical washout with cholestyramine or activated powdered charcoal according to the processes described within the SmPC must be initiated. In the event of unplanned pregnancy LEF should be stopped immediately.

participants wishing to conceive should undergo LEF washout with cholestyramine according to the processes described within the SmPC. For participants who are women of child-bearing potential who do not wish to undergo washout with cholestyramine then contraceptive measures (see appendix 2) must be used for 2 years after the end of trial treatment. In the event of unplanned pregnancy LEF should be stopped immediately (51).

13.4 PROCESSES AND CONSIDERATIONS COMMON TO BOTH DMARDS

13.4.1 Laboratory Abnormalities and Infections

A temporary DMARD treatment interruption may be required (managed at the investigator's discretion) under circumstances such as those described below.

Abnormal LFTs

- ALT or AST elevation of ≥ 3 times ULN, dose interruption is recommended.
- ALT or AST elevation ≥ 5x ULN, discontinuation of DMARD treatment is recommended.
- If ALT or AST elevation of ≥ 3 times ULN and
    - Total bilirubin > 2x ULN or INR > 1.5 ULN, and
    - Alkaline phosphatase > 2x ULN and
    - Presence of worsening fatigue, nausea, vomiting, fever, rash, or eosinophilia,

  discontinuation of treatment is recommended.

Infections

Clinical signs which suggest the possibility of drug toxicity may include severe or frequent minor infections, mucositis and pneumonitis and should be interpreted by the investigator and lead to dose interruption if indicated. Multiple dosing interruptions up to 8 weeks at any one time are allowed if necessary.

Neutropenia

Absolute neutrophil count decrease should be managed according to clinical judgment; a decrease to < $1x10^9$/L (1×10^3 /uL) should however result in treatment interruption. Study treatment should commence after increase of the neutrophil count to ≥ $1x10^9$/L and in line with clinical judgment. Treatment is continued as long as no further safety concerns arise. Multiple dosing interruptions up to 6 weeks at any one time are allowed if necessary.

The participant's welfare is the responsibility of the investigator. Therefore, the investigator must decide, based on risk-benefit assessment, what is needed to ensure the safety of the treatment. These options include deciding when unscheduled or repeat laboratory testing is indicated, and if a temporary interruption or discontinuation of treatment +/- concomitant medication is appropriate.

13.3.2 Cessation of DMARD

Participants are permitted to stop DMARD within the trial once six months have elapsed since they stopped taking steroids.

13.3.3 Procedures if participant transfers to another hospital

The DMARD prescriptions are issued by the hospital Study Site. Therefore, if the participant moves interstate (between South Australia, Western Australia or Victoria), then the local investigator should verify that DMARD prescription and blood monitoring arranged by the Site Research Team can safely continue and transferred providing participants are willing to continue engagement with the follow-up procedures. If the Participant moves to another state, they would have to withdrawn from the study with safety of ongoing / removal of treatment communicated with the participants GP.

13.3.4 Further therapy post-trial

DMARD may be continued beyond the end of the study if clinically indicated and if local procedures allow.

13.4 WITHDRAWAL OF TREATMENT

In line with usual clinical care, cessation or alteration of regimens at any time will be at the discretion of attending clinicians or the participants themselves. All participants withdrawn from treatment or prescribed alternative treatment will still attend for follow-up assessments unless unwilling to do so and eCRFs will continue to be completed.

The PI, or delegate should make every effort to ensure that the specific wishes of any participant who wishes to withdraw consent for further involvement in the trial are defined and documented using the Withdrawal CRF in order that the correct processes are followed by the CTRU and site following the withdrawal of consent. It should be made clear to any participant specifically withdrawing consent for further data collection in a CTIMP that data pertaining to safety will continue to be collected for regulatory reporting purposes and will be included in any safety analysis. In addition, it is suggested that the participant is made aware of the fact that if any significant new information becomes available in regard to the treatment they have received in the trial, it may be necessary to contact them in the future.

14 ASSESSMENTS/SAMPLES/DATA COLLECTION

14.1 SUBMISSION OF TRIAL DATA

Informed Consent Documents, Serious Adverse Events (SAE), Suspected Unexpected Serious Adverse Reaction (SUSAR) and Participant Questionnaire Booklets will be collected via paper case report forms. CTRU will provide an electronic copy of these forms to be printed and completed by research staff at site and the information sent to CTRU, usually by electronic secure file transfer. All other data collection will be via Remote Data Entry (RDE) on electronic case report forms (eCRFs) managed by the CTRU at the University of Leeds. Access to the live STERLING database will be provided by the CTRU following sites being authorised to open to recruitment; guidance on RDE and completing eCRFs will be provided.

Data must only be completed by personnel authorised to do so by the Principal Investigator, as recorded on the trial-specific Authorised Personnel Log.

Where additional documentation is required by CTRU, for example hospital reports and letters, it is the responsibility of staff at research sites to redact all personal identifiable data prior to sending to CTRU. Such records should only include trial number, initials and date of birth to identify the participant. The exception to this is the participant consent form, where the participant's name and signature must not be redacted.

Participating hospitals will be expected to maintain a file of essential trial documentation (Investigator Site File) that will be provided by CTRU, and where applicable, keep copies of all sites completed paper CRFs for the trial (with the exception of QoL & Healthcare Resource use questionnaires).

14.2 SCHEDULE OF EVENTS.

Not included in this table: on reaching below 5mg prednisolone or equivalent for the first time, a 9am cortisol blood test should be performed (sections 14.6 & 14.8).

	Follow-up schedule (weeks);							Telephone Contact (Weeks)	DMARD monitoring blood tests	Blood Pressure (LEF only)
Participant Consent	**Screening**	**Baseline (0)**	**12**	**24**	**36**	**48**	**80**	**4, 8, , 60, 72**	**As per local guidelines †‡**	**As per local guidelines †‡**
Target Visit Window	**Max. 6 weeks between Screening and Baseline**		**-/+ 2 weeks**	**-/+ 2 weeks**	**-/+ 2 weeks**	**-/+ 2 weeks**	**-/+ 2 weeks**			
Written Informed Consent/Witnessed verbal informed consent	x									
Reg and Rand										
Registration	x									
Randomisation		x								
Trial Assessments			**12**	**24**	**36**	**48**	**80**			
Eligibility Checks	x	x								
Steroid Use Review		x	x	x	x	x	x	x		
DMARD Use Review if applicable			x	x	x	x	x	x		
Medical History		x	x	x	x	x	x			
AEs/SAEs review			x	x	x	x	x	x		
Chest X-Ray*	x									
Pregnancy Test	x									
RF§	x									
ACPA§	x									
U&E	x	x	x	x	x	x	x		x	
FBC	x	x	x	x	x	x	x		x	
Liver Function Test	x	x	x	x	x	x	x		x	
HbA1C		x	x	x	x	x	x			
CRP (Also needed for PMR-AS)	x	x	x	x	x	x	x			
ESR		x	x	x	x	x	x			
Physical Examination	x	x	x	x	x	x	x			
Vital Signs	x	x	x	x	x	x	x			
PMR Activity Score		x	x	x	x	x	x			
(PMR-AS) Number of minutes of morning stiffness		x		x			x			
(PMR-AS) Upper limb elevation / active shoulder abduction		x		x			x			
(PMR-AS) VAS global assessment (physician)		x		x			x			

Steroid Free Remission							x			

* a report from a chest x-ray performed within the 6 months prior to the screening visit is acceptable to confirm eligibility providing that no evidence of interstitial lung disease or tuberculosis or active.

† As a guide the British Society for Rheumatology DMARD monitoring guidelines recommend FBC, U+E and LFT: every two weeks until on stable dose for six weeks, then monthly for three months and quarterly thereafter. Blood pressure should be measured at the same timepoints as these blood tests.

‡ Providing the results of the prior test are acceptable (see section 13.4.1), a window will be allowed one week either side of the scheduled date during the first six weeks, two weeks either side of the next scheduled date for the next three months and one month either side of the next scheduled date thereafter

§ Rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA/anti-CCP) both within local laboratory reference range at or within the 12 months prior to the screening visit

14.3 PARTICIPANT QUESTIONNAIRE SCHEDULE

Questionnaires	**0**	**12**	**24**	**36**	**48**	**60**	**72**	**80**
PMR-IS	x	x	x	x	x	x	x	x
Pain VAS (Also needed for PMR-AS)	x		x					x
EQ-5D-5L	x	x	x	x	x	x	x	x
Health Resource Use	x	x	x	x	x	x	x	x
Steroid Use	Every 4 weeks from week 4 to week 80							

14.4 SCREENING ASSESSMENTS

Trial screening assessments should take place after written informed consent has been obtained and after registration on the CTRU 24-hour Registration system has been completed. Trial Screening assessments are designed to establish participant eligibility to enter the trial and include the following assessments listed below.

- Physical examination - cardiorespiratory, abdominal, skin, head/eyes/ENT, and screening neurological exam, as well as MSK system including elevation of upper limbs, joint swelling/tenderness/limitation of movement, and vascular including temporal arteries
- Chest X-Ray: a report from a chest x-ray performed within last 6 months prior to the screening visit is acceptable to confirm eligibility providing that no evidence of interstitial lung disease or tuberculosis or active infection.
- Pregnancy test for women of childbearing potential
- Rheumatoid factor (RF) test – result from any test performed within last 12 months prior to the screening visit is acceptable to confirm eligibility.
- Anti-citrullinated peptide antibody (ACPA) test – result from any test performed within last 12 months prior to the screening visit is acceptable to confirm eligibility.
- Urea & Electrolytes (U&E) test
- Full blood count
- Liver function test
- CRP
- Vital Signs – including, BP, heart rate, temperature

Where local guidelines apply stricter suitability criteria then those listed below then the local criteria should be applied. However, the following should be applied as a minimum/maximum acceptable parameter:

- 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 $x10^9$/L
- 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

Confirmation that the participant meets all other eligibility criteria can be obtained via a combination of i) review of their medical notes or information provided by their GP as part of the referral process and ii) taking the medical history of the participant at the screening visit.

Following the completion of the trial screening assessments, the Eligibility Checklist eCRF should be completed to confirm participant eligibility. All eligible participants should be invited to attend a baseline assessment visit (week 0). If a participant will not be proceeding to randomisation the reason for not proceeding will be captured on the Eligibility Checklist eCRF and no further visits or data collection should be completed.

14.5 BASELINE ASSESSMENTS (WEEK 0)

The baseline assessment should take place for all consenting, registered and eligible participants within 6 weeks of screening. The visit should take place in person. Prior to randomisation the assessments listed below

should be completed and documented on the Baseline Assessments eCRF.

- Participant reported current steroid use
- Relevant medical history
- Urea & Electrolytes (U&E) test
- Full blood count
- Liver function test
- HbA1C test
- CRP test
- ESR test
- Physical examination - MSK system including elevation of upper limbs, joint swelling/tenderness/limitation of movement, and vascular including temporal arteries
- Vital Signs – including, BP, heart rate, temperature
- Weight, hip and waist circumference
- PMR Activity Score (52), requiring:
    - CRP (as stated above).
    - VAS global assessment (physician) (0-10).
    - Number of minutes of morning stiffness.
    - Upper limb elevation / active shoulder abduction (EUL) graded as 0-3.

Participant pain VAS (0-10) (see section 14.10)

In addition, the participant must be given the Participant Baseline Questionnaire Booklet (See section 14.10) to complete before completing the randomisation event on the CTRU 24-hour randomisation system. Persons accessing the randomisation system will be required to confirm that all baseline assessments and questionnaires are complete before randomisation can be completed.

14.6 TELEPHONE ASSESSMENTS WEEK 4, 8, , 60 and 72

Participants will be periodically contacted by the site team via a telephone call to check adherence to the prescribed treatment, collect details of adverse events and any significant changes to medical history or other relevant factors that may affect the administration or dosing of DMARD. For participants in the usual care plus DMARD arm, potential dose escalation will be discussed during the call (see section 13.1.11 for MTX escalation or section 13.2.8).

The data listed below will be collected at this time point.

- Steroid and DMARD use
- (S)AE reporting (including Adverse Events related to glucocorticoid toxicity e.g. infection, diabetes, hypertension and fracture)
- State that DMARD monitoring test results, if applicable, have been reviewed and that the participant is ok to continue ongoing prescribing.
- Whether a 9am cortisol test has been advised and if so the date windows during which it is anticipated that it might be done.

The current steroid dose being taken by the participant, and the participant's current rate of steroid taper, will be used to determine whether the dose is likely to fall below 5mg prednisolone equivalent before the next scheduled study contact. If so, the participant will be advised of the need for a 9am cortisol blood test to screen for possible adrenal insufficiency. This test will be requested in advance by the site study team and the participant will be advised when they will need to have this test done, and

appropriate advice as to how it should be taken (blood to be drawn at 9am at least 24 hours after the most recent steroid dose).

14.7 WEEK 12, 24,36, 48 and WEEK 80 FOLLOW-UP STUDY VISITS

These visits will be conducted in clinic, face to face at 24 and 80 weeks post randomisation. The following data will be collected.

- Steroid and DMARD use
- (S)AE reporting (including Adverse Events related to glucocorticoid toxicity e.g. infection, diabetes, hypertension and fracture)
- Relevant medical history
- Urea & Electrolytes (U&E) test
- Full blood count
- Liver function test
- PMR Activity Score (52), requiring: (week 24 & 80 only)
    - CRP;
    - Physician VAS assessing disease activity;
    - Number of minutes of morning stiffness;
    - Upper limb elevation / active shoulder abduction; (EUL) graded as 0-3
    - Participant pain VAS (0-10) (see section 14.10)
- Weight
- Hip and waist circumference (week 80 only)
- HbA1C test(week 24 & 80 only)

- ESR test
- Physical examination – MSK system including elevation of upper limbs, joint swelling/tenderness/limitation of movement, and vascular including temporal arteries
- Vital Signs – including, BP, heart rate, temperature
- Participant questionnaires (see section 14.10)

14.8 SCREENING FOR POSSIBLE ADRENAL INSUFFICIENCY

At the point that the participants steroid dose drops below 5mg of prednisolone or equivalent for the first time during the trial period, a 9am cortisol test is suggested. Because of the requirement for a 9am blood test, it is likely that participants will prefer to have this done at their local pathology clinic, rather than necessitating a separate hospital visit.

In relation to this test, the data listed below will be collected.

- 9am cortisol test result
- Confirmation of current steroid dose at the time the cortisol test was done.
- Statement that result has been reviewed, and whether participant is judged to be at high, moderate or low risk of adrenal insufficiency; and whether steroid dosing advice has changed in response to this, further testing arranged including repeat 9am cortisol and/or synacthen test, steroid sick day rules provided, and/or discussion with or referral to Endocrinology

14.9 DMARD MONITORING

Participants allocated to MTX and LEF must also undergo the following procedures and information collection in line with local practice in order to determine the safety of these IMPs and to establish if it is safe to continue with the treatment.

As a guide the British Society for Rheumatology DMARD monitoring guidelines recommend FBC, U+E and LFT:

- every two weeks until on stable dose for six weeks
- then monthly for three months
- quarterly thereafter

This data will not be recorded on the CRFs unless it qualifies as an Adverse Event. Please refer to the corresponding schedule of events table for the time points (Section 14.2):

The site team will issue sufficient laboratory request forms to cover the duration of each prescription and will check the results of the monitoring blood tests before each new prescription of MTX is issued.

Subject to agreement of the GP practice, the participant may have the blood draws taken at their GP practice, providing the results can be accessed by the team.

Providing the results of the prior test do not fall outside the limits referred to in section 13.4.1 (and are acceptable according to local physician discretion windows either side of the scheduled blood monitoring dates will be allowed. Please see Schedule of Events for details of appropriate windows.

14.10 PARTICIPANT QUESTIONNAIRES

Participant-reported steroid dose, and whether this needed to be increased due to increase in PMR symptoms, will be collected via the Steroid Use Questionnaire. This questionnaire will be administered every four weeks from week 4 to week 80. Cumulative (prednisolone-equivalent) steroid dose will be estimated from data provided in the Steroid Use Questionnaire, interpolating if necessary. PMR relapse date(s) and date(s) of steroid cessation, if applicable, will be calculated from the data provided in the Steroid Use Questionnaire, allowing time to relapse, number of PMR relapses and time to steroid cessation and time to steroid-free remission to be calculated during the analysis of the trial.

PMR symptom severity will be captured via the PMR-IS administered at baseline (week 0) and weeks 12, 24, 36, 48, 60, 72 and 80 post randomisation.

Participant health related quality of life will be captured via the EQ-5D-5L questionnaire. This will be administered at baseline (week 0) and weeks 12, 24, 36, 48, 60, 72 and 80 post randomisation.

Participant healthcare resource use will be collected at baseline (week 0), and weeks 12, 24, 36, 48, 60, 72 and 80 post randomisation.

In addition, questionnaire booklets at baseline (week 0) and weeks 24 and 80 post baseline will include a Visual Analogue Scale (range 0 to 100mm) on which participants will mark the level of Pain they experience.

This will be used to score the PMR Activity Score. Booklets including this VAS will be distributed separately, as professional printing is required to ensure VAS lengths are exactly 100mm.

Questionnaires completed at baseline (week 0) will be administered by the research staff via a paper booklet before the participant has been informed of the randomisation allocation. Participants will be given the choice of completing questionnaires at all subsequent time points either on paper or electronically. For participants wishing to complete the questionnaires electronically they will be given the option of receiving an email or text message with a link to their questionnaire. Participants' preferred method of questionnaire administration and completion will be collected during the trial randomisation process and applicable contact details, postal address/email address/mobile phone number, collected. The CTRU will send questionnaires to participants directly. Non-respondents will receive reminders by their pre-stated preferred method of communication. The CTRU will contact sites at intervals throughout the study to ensure that consenting participant's contact details and status have not changed and that it is still appropriate to send them a questionnaire.

14.11 DEATHS

All deaths must be recorded on the Notification of Death eCRF and submitted to the CTRU within 7 days of notification to the site trial research team.

All deaths should be assessed to determine whether they meet the criteria of a SAE, SAR or SUSAR. Definitions and reporting requirements for SAEs, SARs and SUSARs can be found in Section 15 of the protocol.

14.12 PARTICIPANT WITHDRAWAL

The PI or delegate should ensure that the specific wishes of any participant who wishes to withdraw consent for further involvement in the trial, be that from further treatment and/or follow-up data collection, are defined and documented using the Withdrawal eCRF in order that the correct processes are followed by the CTRU and site following the withdrawal of consent.

If a participant withdraws consent for further trial treatment and / or further collection of data, their data collected prior to withdrawal of consent will remain on file and will be included in the final study analysis. Data outstanding up to the point of withdrawal will be chased with site. The Participant will be asked to sign a withdrawal of consent form.

It should be made clear to any participant specifically withdrawing consent for further data collection that data pertaining to safety, for example SAEs and SUSARs, will continue to be collected for regulatory reporting purposes and will be included in any safety analysis. In addition, it is suggested that the participant is made aware of the fact that if any significant new information becomes available in regard to the treatment they have received in the trial it may be necessary to contact them in the future.

Where the participant withdraws their consent for completion of participant questionnaires, questionnaires completed prior to withdrawal of consent will be included in the analysis.

If it is the decision of the attending clinician to withdraw the participant from further treatment, then this should also be documented on the Withdrawal eCRF. The trial Schedule of Events and data collection should continue per protocol, unless the participant explicitly withdraws their consent for this.

14.13 PARTICIPANT TRANSFERS

If a participant is being permanently transferred to another site participating in STERLING, then the Participant Transfer eCRF needs to be completed and returned to CTRU as soon as possible to enable appropriate tracking of the participant.

Copies of any paper CRFs, consent forms and any other relevant correspondence is sent to the new hospital, with the originals kept at the original enrolling site. Data queries from events arising before the date of transfer will be directed to the original enrolling site; data queries from events arising after the transfer date will be directed to the new site. Both sites must ensure that the participant transfer is recorded on the participant log in the Investigator Site File.

14.14 PROTOCOL VIOLATIONS

A protocol violation can be defined as: Any accidental or unintentional change to, or non-compliance with the protocol that increases risk or decrease benefit, or has a significant effect on the participant's rights, safety, or welfare, or on the integrity of the data.

Examples of a violation include, but are not restricted to:

- Failure to obtain valid informed consent prior to performing any other trial investigation or procedure.
- Breaches of eligibility criteria.
- Drug administration errors relating to the IMP (e.g. overdose, underdose, not performing specified suitability-for-treatment tests, not modifying dose in line with required modifications).

Protocol violations should be reported immediately to the CTRU using the Protocol Violations eCRF.

The following events do not need to be reported as a protocol violation:

- A rescheduled study visits
- Participant refusal to complete scheduled research activities
- Limited dosing errors by either participant or site, i.e. 1 or 2 that did not result in an SAE and that were deemed not medically significant by site.

Contact details for reporting protocol violations (before or after eCRF entry):
Email: STERLING@LEEDS.AC.UK

14.15 DEFINITION OF END OF STUDY

The end of the trial is defined as the date of the collection of the last participant's last data item. Participants will be followed up until death or until the end of their follow-up period as described in Section 14.6-14.10 (whichever is sooner).

15 PHARMACOVIGILANCE

15.1 GENERAL DEFINITIONS

Adverse Event (AE) - An adverse event (AE) is any untoward medical occurrence in a participant or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Adverse Reaction (AR) - All untoward and unintended responses to an investigational medicinal product related to any dose administered. This definition implies a reasonable possibility of a causal relationship which is supported by facts, evidence or arguments to suggest a causal relationship. This definition includes ARs resulting from a medication error and uses outside what is foreseen in the protocol, including misuse and abuse from the product.

N.B. Medication errors themselves, or misuse/abuse of trial treatment should be notified to CTRU via a protocol violation.

Serious Adverse Event (SAE) - *Any untoward medical occurrence or effect that at any dose:*

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- jeopardised the subject or required intervention to prevent one of the above - hereinafter referred to as 'important medical events (IME)'

Medical and scientific judgement must be exercised in deciding whether an event is serious (see section 15.6 for Responsibilities). These characteristics / consequences must be considered at the time of the event and do not refer to an event which hypothetically may have caused one of the above. For example, life threatening: this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Serious Adverse Reaction (SAR) - reference is made to the criterion of 'Seriousness' above in relation to SAE. (Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.)

Suspected Unexpected Serious Adverse Event (SUSAR) – a SAR, the nature and severity of which is not consistent with the Reference Safety Information (RSI).

Severity describes the intensity of the event. This must be distinguished from the term 'serious'.

Reference Safety Information (RSI) - When determining whether an SAE is expected or not, please refer to section 4.8 of the pharmacovigilance reference copy of the methotrexate or leflunomide (as relevant) Summary of Product Characteristics (SmPC) supplied by CTRU and included in the Investigator Site File. Events appearing in the RSI should be recorded as SARs on the SAE CRF and not as SUSARs, unless the nature, seriousness, severity or outcome is not consistent with the relevant product information.

15.2 OPERATIONAL DEFINITION & REPORTING ADVERSE EVENTS/REACTIONS (AES/ARS)

Information about adverse events/reactions whether volunteered by the participant, discovered by investigator questioning or detected through physical examination, laboratory test or other investigation will be collected and recorded on the relevant Clinical Assessment CRF. All adverse events should be recorded in the participant's medical notes so that they can be followed up if necessary.

This is a randomised controlled trial using treatments with well-known safety profiles already established in the therapy of rheumatological conditions. Although not licensed for PMR, MTX has been shown in clinical practice to be safe and well-tolerated in a PMR population (31). Similarly, in the previous trial by Caporali et al., the main adverse effects that occurred more often in the MTX than placebo arm of the trial was mild gastrointestinal adverse effects. The strategy being tested is DMARD (MTX or LEF) in conjunction with usual care steroid taper, compared to usual care steroid taper alone. The IMPs are defined as the DMARDs, MTX or LEF.

Therefore, the following expected adverse events, related to either tapering of steroid for PMR or to the IMPs, will be reported. It is noted that causality (determination that an Adverse Event is an Adverse Reaction related to a particular IMP) may be difficult to determine since participants will also be receiving other medications, including steroids which should not be stopped abruptly and which can cause many of the adverse events listed below; however, because MTX is administered weekly, assessment of causality may be facilitated by temporality of symptoms in relation to MTX administration

15.2.1 Expected AEs potentially related to tapering of steroid for PMR:

- Diagnosis of adrenal insufficiency – see section 17.2.2
- Diagnosis of giant cell arteritis

15.2.2 Expected AEs/ARs potentially related to MTX:

Please report the following if severity is consistent with **CTCAE grade 2 and above (see Appendix 3)**:

- Clinically significant deranged liver function test values (as judged by the local investigator)
- Clinically significant cytopenia (as judged by the local investigator)
- Depression (diagnosis of depression, or initiation or increase of depression medication)
- Infection (infection requiring treatment with oral, IV or IM antibiotics, or any episode of shingles, or a positive community test for COVID-19)
- Mucositis oral (participant reported)
- Nausea (participant reported)
- Abdominal pain (participant reported)
- Diarrhoea (participant reported)
- Hair thinning/alopecia (participant reported)
- Headache (participant reported)
- Fatigue (participant reported)

15.2.3 Expected AEs/ARs potentially related to LEF:

Please report the following if severity is consistent with **CTCAE grade 2 and above (see Appendix 3)**:

- Clinically significant deranged liver function test values (as judged by the local investigator)
- Clinically significant cytopenia (as judged by the local investigator)
- Hypertension (requirement for new antihypertensive medication or increased dose of current antihypertensive medication)
- Infection (infection requiring treatment with oral, IV or IM antibiotics, or any episode of shingles, or a positive community test for COVID-19)
- Mucositis oral (participant reported)
- Nausea (participant reported)
- Abdominal pain (participant reported)
- Diarrhoea (participant reported)
- Hair thinning/alopecia (participant reported)
- Paraesthesia (participant reported)
- Rash maculo-papular (participant reported)
- Headache (participant reported)
- Fatigue (participant reported)

These should be reviewed and classed by a clinically qualified person to assess for causality and expectedness.

15.3 OPERATIONAL DEFINITION - SERIOUS ADVERSE EVENTS/REACTIONS (SAEs/SARs)

It is acknowledged that this patient group are likely to experience numerous adverse events related to co-morbidities other than PMR or its treatment. In acknowledgement of this and the well-known safety profile of DMARDs, in this study only serious adverse events that are suspected to be related to PMR or the IMPs will be reported.

15.3.1 Events not reported as SAEs/SARs

The following events will not be classified as SAEs

Hospitalisation for:

- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- Treatment, which was elective or pre-planned, for a pre-existing condition, not associated with any deterioration in condition e.g. pre-planned hip replacement operation, which does not lead to further complications.
- Treatment on an emergency, outpatient basis for an event **not** fulfilling any of the definitions of serious as given above and not resulting in hospital admission.

15.4 RECORDING AND REPORTING AEs, ARs, SAEs, SARs AND SUSARs

Monitoring for safety events should commence on the date of consent and continue until a minimum of 30 days post last dose of randomised treatment.

AEs and SAEs will be collected on the relevant eCRF and reported to CTRU from the date of consent and continue until a minimum of 30 days post last dose of randomised treatment.

Reporting of ARs, SARs and SUSARs to CTRU should commence on the date of the first IMP dose taken and continue until a minimum of 30 days post last dose of randomised treatment.

15.4.1 SAEs AND SARs

All SAEs, SARs and SUSARs must be recorded on the SAE eCRF (in the case of SAEs and SARs) or SUSAR eCRF as appropriate and sent by secure file transfer to the CTRU via secure file transfer **within 24 hours** of the research staff becoming aware of the event.

Assessment of causality and expectedness must be made by an authorised physician. If an authorised physician is unavailable, initial reports without causality and expectedness assessment should be submitted to CTRU but must be followed up by medical assessment as soon as possible thereafter.

The original SAE/SUSAR Report CRF(s) should be retained by site until the event has reached a final outcome and all queries have been resolved (as determined by CTRU). When requested, please return original (wet-ink) initial and follow-up reports to CTRU and retain copies at site.

Each SAE will be described by:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial drug or PMR) in the opinion of the investigator
- whether the event would be considered expected or unexpected

Changes in outcome, seriousness criteria, causality, or significant / medically relevant changes to the event (key data) should be sent by secure file transfer to CTRU within 24 hours of becoming aware. Other follow up information should be sent by secure file transfer to CTRU when the event has reached a final outcome, or when requested. Events will be followed up until the event has resolved or a final outcome has been reached.

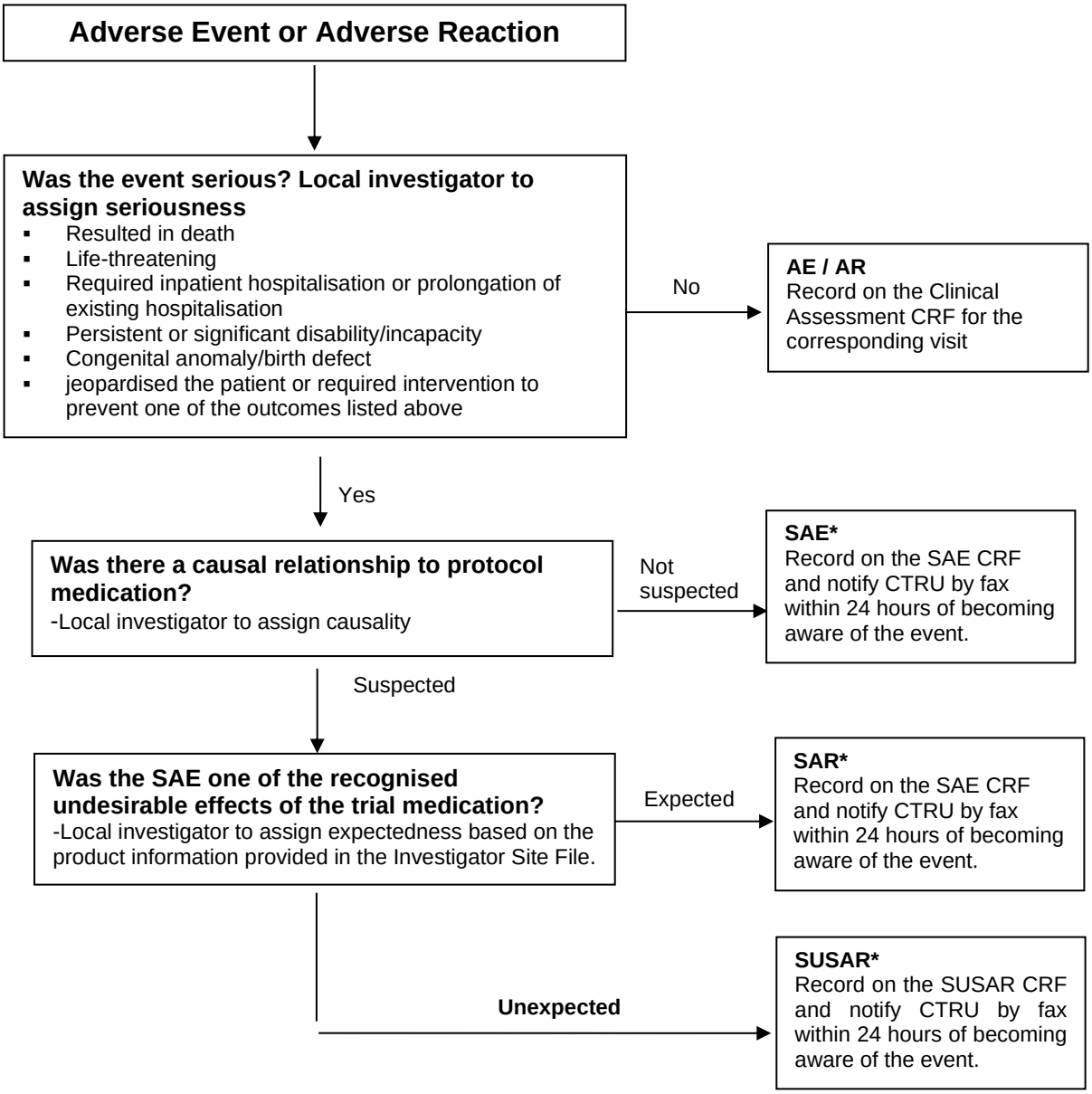
Please ensure that each SAE/SAR/SUSAR event is reported separately and not combined on one form.

Investigators must report all SAEs to their host institution in line with their local arrangements.

15.4.2 SUSARs

All SAEs assigned by the PI or delegate (or following central review) as both suspected to be related to IMP-treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the Medicines and Healthcare products Regulatory Authority (MHRA). The CTRU will inform the MHRA, the main REC and the Sponsor of SUSARs within the required expedited reporting timescales.

15.5 OVERVIEW OF THE SAFETY REPORTING PROCESSES



Pregnancies
Site staff should notify the CTRU of a pregnancy in a trial subject or the partner of a trial subject and the estimated due date immediately on the Notification of Pregnancy CRF.

** The following events should also be regarded as SAEs in participants receiving **abatacept**: **1)** Cancer **2)** Overdose leading to an SAE **3)** Pregnancy **4)** Medication error leading to an SAE **5)** Suspected transmission of an infectious agent via the drug **6)** Potential Drug Induced Liver Injury (DILI).

*The Chief Investigator (or delegate) will review all received SUSARs for seriousness, expectedness and causality. All SUSARs or increase in trends or severity of SARs will be identified and expeditiously reported to the MREC, MHRA and Sponsor.

15.6 PREGNANCY

Pregnancy in participants participating in this study must be prevented as effectively as possible.
Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease status) in a participant occurring during the trial must be recorded on the Notification of Pregnancy Form and sent by secure file transfer to the CTRU **within 24 hours** of the research staff becoming aware of the event.

Pregnant participants must be followed until the end of their pregnancy and the CTRU must be notified of the outcome of the pregnancy (including false-positive pregnancy tests) within 24 hours of this information being known. If a pregnancy occurs in a male participant's partner, details of the pregnancy will still be collected where possible and the outcome of the pregnancy must be notified to CTRU.

The outcome of any pregnancy which qualifies as a SAE (i.e. spontaneous or therapeutic abortion, foetal and neonatal death, or congenital abnormalities – including those detected in an aborted foetus), birth defects, or the death of an infant which occurs in connection with in utero exposure to the study drugs must be reported to the CTRU as a SAE in accordance with Section 15.4.1

All DMARD treatment must be stopped immediately if a pregnancy in a female participant occurs or is suspected. Relevant clinical guidelines should be followed. At the time of writing this includes the 2022 British Society for Rheumatology guidelines (53) and the 2020 American College of Rheumatology guidelines (54); for MTX it is advised to stop MTX and commence folic acid 5mg daily whereas for LEF cholestyramine washout and measurement of post-washout LEF levels is advised.

Participants withdrawn from treatment will still attend for follow-up assessments unless unwilling to do so and case report forms will continue to be collected. Pregnant female participants should be referred to an obstetrician/gynaecologist experienced in reproductive toxicity for further evaluation and counselling. The pregnancy will be followed up until final outcome (termination of pregnancy, miscarriage, stillbirth or live birth).

15.6 RESPONSIBILITIES

Principal Investigator (or delegate) at site:

- Checking for AEs/SAEs during telephone follow-up assessments
- Checking for AEs/SAEs when participants attend for treatment / follow up.
- Using medical judgement in assigning seriousness, causality and expectedness using the Reference Safety Information approved for the trial.
- To ensure all SAEs and SARs (including SUSARs) are recorded and reported to the CTRU within 24 hours of becoming aware of the event and to provide further follow up information as soon as available. Ensuring that SAEs and SARs (including SUSARs) are chased with CTRU if a record of receipt is not received within 2 working days of initial reporting.
- Ensuring that AEs and ARs are recorded and reported to the CTRU in line with the requirements of the protocol.

- Communication to the GP of any clinically relevant change in the participant's medical condition that might affect their ongoing care, including management of co-morbidities.

Chief Investigator (or nominated individual in CI's absence):

- Clinical oversight of the safety of trial participants, including an ongoing review of the risk / benefit.
- Using medical judgment in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
- Immediate review of all SUSARs.
- Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
- Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.
- Preparing the clinical sections and final sign-off of the Development Safety Update Report (DSUR).

CTRU:

- Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a MACRO database.
- Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
- Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring & Ethics Committee (DMEC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
- Expedited reporting of SUSARs to the Competent Authority (MHRA in UK), main REC and Sponsor within required timelines.
- Notifying Investigators of SUSARs that occur within the trial.
- Reporting events to collaborating pharmaceutical company in accordance with the trial contract.
- Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.
- Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and Main REC.

TSC:

- In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMEC regarding safety issues.

DMEC:

- In accordance with the Trial Terms of Reference for the DMEC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

16 OUTCOME MEASURES

16.1 PRIMARY OUTCOME MEASURE

The primary outcome measure is mean participant reported cumulative prednisolone dose between randomisation and 18 months post-randomisation, reported by participants via a monthly questionnaire.

Where a participant receives an alternative steroid medication to prednisolone, the steroid dose will be converted to a "Prednisolone equivalent dose" prior to analysis.

Intercurrent events of interest are:

- Death – to be handled under a treatment policy strategy;
- Discontinuation of trial treatment (including crossover to other arm) – to be handled under a treatment policy strategy;

Although steroid diaries are a part of routine clinical care, we acknowledge a lack of data as to the accuracy of participant-completed steroid diaries as a means to track medication usage. We have identified only small-scale results, incompletely reported and for different populations, claiming that medication diaries have satisfactory test-retest reliability (62)and that comparable methods of medication use surveillance lead to similar reported adherence levels (63).

16.2 SECONDARY OUTCOME MEASURES

16.2.1 Participant reported outcomes

16.2.1.1 PMR Symptom Severity – Mean PMR-IS Symptom domain score, Mean PMR-IS Symptom function score, Mean PMR-IS Psychological/Emotional well-being domain score, Mean PMR-IS Steroid side effect domain score – all at each of the timepoints [Weeks 12, 24, 36, 48, 60, 72, 80 post randomisation]

PMR-Impact Scale (PMR-IS) comprises four domains: symptoms, function, psychological and emotional well-being, and steroid side effects (64, 65). Scores are presented separately for each domain to aid clinical utility. In each domain, the domain score is derived as the mean of the item responses, converted to a percentage (0-100) with higher scores representing better status domain.

None of the domains of the PMR-IS has been identified as being of a priori importance.

16.2.1.2Health-related Quality of Life – Mean EQ-5D-5L Utility [Weeks 12, 24, 36, 48, 60, 72, 80 post randomisation]

The five categorical domain responses to the EQ-5D-5L will be converted to a utility score, following the value set approved by NICE.

At time of protocol v1.0, the approved mapping of responses to utilities is following the Crosswalk algorithm of van Hout et al (66). Should NICE approve an alternative value set, this will be used instead.

16.2.1.3 PMR Disease Activity (Mean PMR Activity Score (PMR-AS) at weeks 4, 24 and 80)

The PMR-AS (ref) is a composite measure, derived from the following clinical and participant-reported measures:

* C-reactive protein (CRP, mg/dL)
* Participant-reported pain, assessed on a visual analogy scale (VASp, range 0 to 10)
* Duration of morning stiffness (MS; in minutes)
* Upper limb elevation (active shoulder abduction, ULE range 0 to 3)
* Physician disease activity assessed on a VAS (VASph, range 0 to 10).

The derivation is PMR-AS = CRP + VASp + (MS×0.1) + ULE + VASph.

16.2.2 Clinical outcomes

Time to steroid cessation

Time to steroid cessation, will be defined as the duration between date of randomisation and date at which participants report a current prednisolone 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.

Participants that have continued to take steroids/prednisolone to the end of follow-up or who had a temporary cessation of steroids will be censored at 18 months. Those who die, withdraw and/or are lost to follow-up will be censored at the point of death/withdrawal or loss to follow-up.

Time to steroid-free remission

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.

Time to 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 whether they have had to adjust their planned steroid dosing plan due to an increase in PMR symptoms (participant reported relapse).

Time to PMR relapse will be defined as the duration between randomisation and date of PMR relapse. Participants that have not relapsed during follow-up will be censored at 18 months, or at date of death or withdrawal.

Note: There is no universally agreed definition of relapse in PMR, therefore, a pragmatic approach will be taken.

Number of PMR relapses

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.

Cumulative (prednisolone-equivalent) steroid dose prescribed
Cumulative (prednisolone-equivalent) steroid dose prescribed over 18 months post randomisation.

The total amount of oral steroid prescribed during the trial will be assessed from GP records of all prednisolone prescriptions issued during the trial, and will be collected at 18 months post randomisation.

As for the primary outcome, if any steroid medications other than prednisolone are prescribed, these will be converted to an agreed "prednisolone equivalent dose" prior to analysis.

Safety
Adverse events (AEs) of Special Interest reported over 18 months post randomisation will include those relevant to PMR and/or investigational medicinal product.

Serious adverse events (SAEs) and SUSARs regardless of relationship to PMR or investigational product reported over 18 months post randomisation.

Glucocorticoid toxicity
Glucocorticoid toxicity is defined as per the OMERACT Glucocorticoid Core Domain Set (infection, diabetes, hypertension, fracture) adapting measures from the Glucocorticoid Toxicity Index (67)

Time to development of GCA
Time to development of GCA (defined as rheumatologist-confirmed and treated according to GCA treatment protocols specified in 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 date of death or withdrawal.

Proportion of participants diagnosed with adrenal insufficiency
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 9am cortisol test, or an intermediate value followed by a positive short synacthen test, at any point during follow-up. Adrenal insufficiency screening tests (9am 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.

Deaths
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.

17. STATISTICAL CONSIDERATIONS

Sample size

In UK primary care (Clinical Practice Research Datalink), patients with relapsing PMR had a mean cumulative prednisolone dose of 5g over 18 months (coefficient of variation (CV) 0.78) (68).

A clinically relevant reduction is benchmarked against the reduction likely to substantively reduce the risk of fracture or infection. Extrapolating from observational data, an average reduction in cumulative prednisolone dose of 1.5g (a reduction in mean daily dose of 2.7mg over 18 months) would be predicted to significantly reduce hip and vertebral fracture risk (69). This corresponds to a 30% reduction in cumulative dose. Our PPI group helped inform this target effect size: discussions around trade-offs revealed that most would not consider a DMARD worth it unless it could substitute for more than 2.5mg daily prednisolone over an 18-month period.

Assuming a log-normal distribution, 200 participants will provide 90% power to detect a target 30% reduction in cumulative prednisolone dose, assuming a CV of 0.78, 2-sided independent t-test for fold change (H0: mean fold change=1), 5% significance and 20% attrition (24) (nQuery v3.0). The trial will retain at least 80% power if the CV is as large as 0.94.

As part of this Australia is recruiting 50 participants there for 25% of the total number for the study.

Planned recruitment rate

Recruitment from secondary care: there will be 3 sites. Each site is expected to be open and recruiting participants over a 12-month period.

We estimate a 3:1 screen: recruitment ratio as being realistic. From the PCRN route plus referrals from rheumatologists, GPs and self- referrals, it is estimated that 150participants will attend screening visits and 50 will be randomised in Australia.

18. STATISTICAL ANALYSIS

18.1 GENERAL CONSIDERATIONS

A full statistical analysis plan (SAP) will be in place prior to any comparative analyses according to guidelines (70) The statistical analysis is the responsibility of the CTRU Statistician and will not include the economic evaluation (section 16). All analyses and patient populations will be predefined in the SAP.

The intention to treat (ITT) population will include all randomised patients, to be analysed in groups assigned at randomisation. A per-protocol population will be defined accounting for major protocol deviations, relating to intervention compliance, eligibility and other criteria agreed by the Trial Management Group prior to any unblinded efficacy analyses. Participants in the Per-Protocol population will be analysed according to randomised allocation.

Primary analysis will be conducted on the intention-to-treat (ITT) population; a secondary per-protocol population analysis will also be undertaken. Statistical monitoring of safety data and underlying assumptions of the statistical design will be conducted and reported to the Data Monitoring and Ethics Committee (DMEC) according to an agreed DMEC Charter.

At the time of the final analysis, the trial will be analysed and reported according to the CONSORT reporting standards (71).

18.2 ANALYSIS OF PRIMARY OUTCOME MEASURE

The primary analysis on log (cumulative prednisolone-equivalent dose reported over 18 months) will use multivariable linear regression, with covariates for the minimisation factors (listed in Section 11.3); age at randomisation will be retained as a continuous covariate, under transformation as necessary. Adjusted mean fold difference in cumulative prednisolone dose will be presented with 95% confidence interval (CI) and significance. Summaries on mean fold difference and absolute difference in cumulative prednisolone dose will be presented.

18.3 ANALYSIS OF SECONDARY OUTCOME MEASURES

PMR symptom severity measures, PMR activity score, and Patient-reported quality of life measures over 18 months: analysis of PMR-IS domain scores, health-related quality of life (EQ-5D-5L Utility), PMR-Activity Score will use multivariable repeated measures linear regression adjusting for minimisation factors, baseline value, treatment group, baseline-by-time interaction (if appropriate), age, time, and time-by-treatment group interaction. Centre will be fitted as a random effect, if feasible and has a positive variance component. Time will be fitted as a continuous variable, and the estimated time-by treatment interaction effect with 95% CI and significance will be presented.

Time to steroid cessation, Time to PMR relapse: time to event will be calculated and summarised using Kaplan-Meier estimates. Adjusted hazard ratios will be estimated using Cox proportional hazards regression or parametric alternative, with covariates for minimisation factors (fitting centre as a random effect, if feasible) age and treatment group, and reported with 95% CI.

Steroid free remission at week 80 post randomisation will be summarised by treatment group and overall.

Number of relapses over time: A multivariable negative binomial regression model will be used to explore the number of relapses reported over follow-up time with an offset term for time at risk, adjusting for minimisation factors, age and treatment group. Centre random effects will be explored, assuming a Gamma distribution. Adjusted difference in rate of relapse with 95% CI will be reported.

Cumulative prednisolone-equivalent dose prescribed: A multivariable linear regression model will be fitted to log (cumulative glucocorticoid dose), adjusting for minimisation factors (fitting centre as a random effect, if feasible) age and treatment group. Adjusted mean fold difference in cumulative glucocorticoid dose with 95% CI will be reported.

Safety: The number of adverse events of special interest related to PMR or trial treatment, serious adverse events and SUSARs, in number of unique patients, will be reported by treatment received (MTX/LEF/Both/Neither) and by severity.

Time to development of GCA will be summarised using Kaplan-Meier estimates. Adjusted hazard ratios will be estimated using Cox proportional hazards regression or parametric alternative, with covariates for minimisation factors (fitting centre as a random effect, if feasible) age and treatment group, and reported with 95% CI.

Adrenal insufficiency: The proportion of participants considered to be experiencing adrenal insufficiency will be reported in both groups.

Deaths: Number of deaths from all causes over 18 months post randomisation and time to death will be summarised by treatment received

18.4 PRE-SPECIFIED EXPLORATORY ANALYSES

To classify symptom trajectories in relapsing PMR using methods exploring correlation structures and 'groupings' of symptoms, summary statistics of baseline characteristics and / or responses to participant-completed questionnaires and other clinic outcomes will be presented. More detailed analyses will be detailed in the analysis plan.

To describe characteristics of participants switching from MTX to LEF and time and reasons for switching, summary statistics of baseline characteristics will be explored between groups who switch and do not switch.

To describe effectiveness of MTX vs LEF (within the DMARD arm) certain outcome measures will be reanalysed, only including participants randomised to the DMARD arm. The treatment group parameter will be replaced with an indicator variable corresponding to the chosen DMARD. If feasible, analysis models will first include terms that are necessary for any multi-level modelling, then where possible terms for the minimisation factors and age.

To explore potential baseline predictors of adverse outcomes, attention will be restricted to only those events reported most frequently. Since the full study sample size may have limited scope to develop robust multivariable prediction models, models will be limited in the numbers of variables included, to reduce the risk of overfitting. Appropriate parameters to permit sample size calculation of cohort sizes needed to develop such a model will be reported. (72).

To describe inflammatory markers and steroid dose at time of relapse, summary statistics of inflammatory markers and steroid dose at the timepoint closest to relapse will be reported.

18.5 MISSING DATA

Missing outcome data may be imputed dependent on level of missingness and reasons for missingness assessing the assumption of missing at random. Sensitivity analyses will report under different assumptions about the missing data.

18.6 INTERIM ANALYSES

No formal interim analyses of efficacy will be performed, and no formal guidelines for stopping the trial early are in place (precluded by the follow-up and recruitment timelines).

Summary reports will be presented on an annual basis to the DMEC who will monitor primarily safety outcomes and data quality as well as the underlying assumptions of the statistical design (specifically, the variability on the primary outcome measure). Analyses will be agreed and documented upfront by the independent DMEC members.

Recommendations made by the DMEC will be expedited to the MHRA where they are deemed relevant for the safety of participants within the trial.

19. TRIAL MONITORING

19.1 TRIAL STEERING COMMITTEE AND DATA MONITORING AND ETHICS COMMITTEE

A Trial Monitoring Plan will be developed and agreed by the Trial Management Group (TMG) and TSC based on the trial risk assessment; this may include on site monitoring.

19.2 TRIAL STEERING COMMITEE (TSC)

The independent TSC have overall responsibility for the external oversight of the trial. The TSC will provide overall monitoring of the trial, in particular trial progress, adherence to protocol, participant safety and consideration of new information. The TSC meeting will be conducted to an agreed TSC Charter, and members will be provided with reports prepared by CTRU. The independent committee will meet at least annually and will consider recommendations made by the independent DMEC.

19.3 DATA MONITORING AND ETHICS COMMITTEE (DMEC)

An independent DMEC will review the safety of participants in the trial by reviewing interim data during the recruitment phase. The DMEC meeting will be conducted to an agreed DMEC Charter, and members will be provided with reports prepared by CTRU. The DMEC meeting will consist of open and closed sessions to discuss aggregate data and, in the closed session, data presented by randomised group or treatment received as appropriate. The DMEC will review the underlying assumptions of the statistical design to ensure the trial remains adequately powered. The Committee will meet annually as a minimum and make recommendation regarding continuation, specifically following the internal pilot phase to the TSC.

19.4 DATA MONITORING

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until it is received, confirmed as not available or the trial is at analysis. However missing data items will not be chased from participants (although missing questionnaires sometimes are). The CTRU and Sponsor will reserve the right to intermittently conduct source data verification exercises on a sample of participants, which will be carried out by staff from the CTRU or Sponsor. Source data verification will involve access to participant notes at the participating hospital sites and the ongoing central collection of copies of consent forms and other relevant investigation reports.

19.5 CLINICAL GOVERNANCE ISSUES

To ensure responsibility and accountability for the overall quality of care received by participants during the study period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the TSC and, where applicable, to individual NHS Trusts, and Human Research Ethics committee.

20. QUALITY ASSURANCE AND ETHICAL CONSIDERATIONS

20.1 QUALITY ASSURANCE

The trial will be conducted in accordance with the principles of Good Clinical Practice (GCP) in clinical trials, as applicable under UK and Australian regulations, the NHS Research Governance Framework (RGF) and Scottish Executive Health Department Research Governance Framework for Health and Social Care 2006 and through adherence to CTRU Standard Operating Procedures (SOPs).

20.2 SERIOUS BREACHES

CTRU and Sponsor have systems in place to ensure that serious breaches of GCP or the trial protocol are picked up and reported. Investigators are required to promptly notify the CTRU of a serious breach (as defined in Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments) that they become aware of. A 'serious breach' is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial.

In the event of doubt or for further information, the Investigator should contact the Senior Trial Coordinator at the CTRU.

20.3 ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 52nd World Medical Association General Assembly, Edinburgh, Scotland, 1996. Informed written consent will be obtained from the participants prior to registration into the study. The right of a participant to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment. The study will be submitted to and approved by a Human Research Ethics committee and the appropriate Site Specific governance for each participating centre prior to entering participants into the study. The CTRU will provide the Human Research Ethics committee with a copy of the final protocol, participant information sheets, consent forms and all other relevant study documentation.

21. CONFIDENTIALITY

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the CTRU. The CTRU will comply with all aspects of the 1998 Data Protection Act and operationally this will include:

- Consent from participants to record personal details including name, date of birth, address and telephone number, NHS number/ CHI number, GP name and address
- Appropriate storage, restricted access and disposal arrangements for participant personal and clinical details
- Consent from participants for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial

participation.

- Consent from participants for the data collected for the trial to be used to evaluate safety and develop new research.
- Participant name, address and telephone number will be collected when a participant is randomised into the trial but all other data collection forms that are transferred to or from the CTRU will be coded with a trial number and will include two participant identifiers, usually the participant's initials and date of birth.
- Where central monitoring of source documents by CTRU (or copies of source documents) is required (such as scans or local blood results), the participant's name must be obliterated by site before sending and labelled with only trial number, participant's initials and date of birth.
- Where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to CTRU.
- Where a third party is involved in the delivery of the trial the University of Leeds will ensure participant information is safeguarded, and an appropriate confidentiality and data security agreement will be put in place.

If a participant withdraws consent from further trial treatment and / or further collection of data their samples will remain on file and will be included in the final study analysis.

22. ARCHIVING

At the end of the trial, all data held by the CTRU and all trial data within the UK will then be securely archived at the University of Leeds in line with the Sponsor's procedures, for a minimum of 25 years. Data held by the CTRU will be archived in the Leeds Sponsor archive facility and site data and documents will be archived at the participating centres. Data held at Australian Sites will be archived at each site, for a minimum of 25 years. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made. If a participant withdraws consent for their data to be used, it will be confidentially destroyed.

23. STATEMENT OF INDEMNITY

This study is sponsored by the University of Leeds and the University of Leeds will be liable for negligent harm caused by the design of the study. The NHS has a duty of care to participants treated, whether or not the participant is taking part in a clinical study and the NHS remains liable for clinical negligence and other negligent harm to participants under this duty of care.

24. STUDY ORGANISATIONAL STRUCTURE

24.1 INDIVIDUALS AND INDIVIDUAL ORGANISATIONS

Chief Investigator (CI) – The CI is involved in the design, conduct, co-ordination and management of the trial. The CI will have overall responsibility for the design and set-up of the trial, the investigational drug supply and pharmacovigilance within the trial.

Trial Sponsor – The Sponsor is responsible for trial initiation management and financing of the trial as defined by Directive 2001/20/EC. In the UK, these responsibilities are delegated to the CTRU as detailed in the trial contract. In the case of Australian sites there is a separate local Sponsor (University of Adelaide/ Austin Health / University of Western Australia).

Clinical Trials Research Unit – The CTRU will have responsibility for conduct of the trial as delegated by the UK Sponsor in accordance with relevant GCP standards and CTRU SOPs. The CTRU will provide set-up and monitoring of trial conduct to CTRU SOPs, and the GCP Conditions and Principles as detailed in the UK Medicines for Human Use (Clinical Trials) Regulations 2006 including, randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, monitoring schedule and statistical analysis for the trial. In addition, the CTRU will support main REC, Site Specific Assessment and NHS Permissions submissions and clinical set-up, ongoing management including training, monitoring reports and promotion of the trial. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses.

24.2 OVERSIGHT / TRIAL MONITORING GROUPS

Trial Management Group (TMG) – The TMG, comprising the CI, CTRU team, other key external members of staff involved in the trial and at least one Participant representative will be assigned responsibility for the clinical set-up, on-going management, promotion of the trial, and for the interpretation and publishing of the results. Specifically the TMG will be responsible for (i) protocol completion, (ii) CRF development, (iii) obtaining required approvals, (iv) submitting a CTA application and obtaining approval from the MHRA, (v) completing cost estimates and project initiation, (vi) nominating members and facilitating the TSC and DMEC, (vii) reporting of serious adverse events, (viii) monitoring of screening, recruitment, treatment and follow-up procedures, (ix) overseeing consent procedures, data collection, trial end-point validation and database development.

Trial Steering Committee (TSC) – The TSC, with an independent Chair, will provide overall supervision of the trial, in particular trial progress, adherence to protocol, participant safety and consideration of new information. It will include an Independent Chair, not less than two other independent members and a consumer representative. The CI and other members of the TMG may attend the TSC meetings and present and report progress. The Committee will meet annually as a minimum.

Data Monitoring and Ethics Committee (DMEC) – The DMEC will include independent membership and will review the safety and ethics of the trial by reviewing interim data during recruitment. The Committee will meet annually as a minimum.

24.2.1 Management of International Sites

Division of responsibilities relating to data management at international sites

The University of Leeds/CTRU will provide access to the database and randomisation along with ongoing maintenance of the database. Australian will have an managing clinical trial coordinator who will monitor the Australian data. Data collected from international sites will be pooled with the UK data for analysis of the trial endpoints.

22.3 Co enrolment with A4BC

Participants will be asked to co enrol into A3BC . The A3BC's integrated collection of longitudinal blood, tissues and other samples with patient-reported outcomes, clinical records and a broad range of state and Commonwealth health datasets, will support complex analyses for more precise prevention, diagnosis, treatment and prognosis through unspecified musculoskeletal and autoimmune research.

25. PUBLICATION POLICY

The trial will be registered with an authorised registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines, prior the start of recruitment.

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributorship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data,
- drafting the article or revising it critically for important intellectual content,
- and final approval of the version to be published,
- and that all these conditions must be met (www.icmje.org).

In light of this, the Chief Investigator, Research Fellow [*include if appropriate*] and relevant senior CTRU staff will be named as authors in any publication. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial.

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the analysis of the primary endpoint, either for trial publication or oral presentation purposes, without the permission of the Trial Steering Committee. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the trial until the first publication of the analysis of the primary endpoint.

APPENDIX 1

Glucocorticoid (steroid) prednisolone equivalent doses

For the purposes of conduct and analysis of this clinical trial, including randomisation minimisation procedures, data collection (determination of current dose), calculation of cumulative prednisolone-equivalent dose, and analysis of safety data where relevant, equivalences of oral prednisolone will be defined as follows.

5mg of oral prednisolone is considered to be equivalent to:

- 5mg of oral prednisone
- 20mg of oral or intravenous hydrocortisone
- 4mg of oral, intravenous, intramuscular or intra-articular methylprednisolone
- 4mg of intravenous, intramuscular or intra-articular triamcinolone
- 0.8mg of oral or intravenous dexamethasone

For most purposes of the conduct and the analysis of the trial, inhaled, intranasal and topical glucocorticoids (steroids) will be assumed to be equivalent to 0mg oral prednisolone.

It should be noted that there is a risk that prolonged or repeated treatment with non-oral glucocorticoid, particularly fluorinated compounds, could contribute to glucocorticoid toxicity including the potential for iatrogenic adrenal insufficiency.

APPENDIX 2

Birth control methods which may be considered as highly effective

For the purpose of this protocol, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods.

- combined (oestrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal
- progesterone-only hormonal contraception associated with inhibition of ovulation:
    - oral
    - injectable
    - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner [3]
- sexual abstinence [4]

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[3] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success.

[4] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

APPENDIX 3

Common Terminology Criteria For Adverse Events (CTCAE)

Events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events V5.0 (NCI-CTCAE). A copy is provided in the Investigator Site File and may be obtained at:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

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REFERENCES

1. Owen CE, Liew DFL, Buchanan RRC. Musculotendinous Inflammation: The Defining Pathology of Polymyalgia Rheumatica? J Rheumatol. 2019;46(12):1552-5.
2. Mackie SL, Pease CT, Fukuba E, Harris E, Emery P, Hodgson R, et al. Whole-body MRI of patients with polymyalgia rheumatica identifies a distinct subset with complete patient-reported response to glucocorticoids. Ann Rheum Dis. 2015;74(12):2188-92.
3. Pujades-Rodriguez M, Duyx B, Thomas SL, Stogiannis D, Smeeth L, Hemingway H. Associations between polymyalgia rheumatica and giant cell arteritis and 12 cardiovascular diseases. Heart. 2016;102(5):383-9.
4. Partington RJ, Muller S, Helliwell T, Mallen CD, Abdul Sultan A. Incidence, prevalence and treatment burden of polymyalgia rheumatica in the UK over two decades: a population-based study. Annals of the Rheumatic Diseases. 2018;77(12):1750-6.
5. van der Geest KSM, Sandovici M, Brouwer E, Mackie SL. Diagnostic Accuracy of Symptoms, Physical Signs, and Laboratory Tests for Giant Cell Arteritis: A Systematic Review and Meta-analysis. JAMA Internal Medicine. 2020;180(10):1295-304.
6. Mackie SL, Dejaco C, Appenzeller S, Camellino D, Duftner C, Gonzalez-Chiappe S, et al. British Society for Rheumatology guideline on diagnosis and treatment of giant cell arteritis. Rheumatology. 2020;59(3):e1-e23.
7. Mackie SL, Hensor EMA, Haugeberg G, Bhakta B, Pease CT. Can the prognosis of polymyalgia rheumatica be predicted at disease onset? Results from a 5-year prospective study. Rheumatology. 2010;49(4):716-22.
8. Floris A, Piga M, Chessa E, Congia M, Erre GL, Angioni MM, et al. Long-term glucocorticoid treatment and high relapse rate remain unresolved issues in the real-life management of polymyalgia rheumatica: a systematic literature review and meta-analysis. Clinical Rheumatology. 2022;41(1):19-31.
9. Dasgupta B, Borg FA, Hassan N, Barraclough K, Bourke B, Fulcher J, et al. BSR and BHPR guidelines for the management of polymyalgia rheumatica. Rheumatology (Oxford). 2010;49(1):186-90.
10. Dejaco C, Singh YP, Perel P, Hutchings A, Camellino D, Mackie S, et al. 2015 Recommendations for the management of polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. Annals of the Rheumatic Diseases. 2015;74(10):1799-807.
11. Gabriel SE, Sunku J, Salvarani C, O'Fallon WM, Hunder GG. Adverse outcomes of antiinflammatory therapy among patients with polymyalgia rheumatica. Arthritis Rheum. 1997;40(10):1873-8.
12. Mazzantini M, Torre C, Miccoli M, Baggiani A, Talarico R, Bombardieri S, et al. Adverse events during longterm low-dose glucocorticoid treatment of polymyalgia rheumatica: a retrospective study. J Rheumatol. 2012;39(3):552-7.
13. Kay LL, P. MacGregor, A. Rheumatology GIRFT Programme National Specialty Report 2021.
14. Hutchings A, Hollywood J, Lamping DL, Pease CT, Chakravarty K, Silverman B, et al. Clinical outcomes, quality of life, and diagnostic uncertainty in the first year of polymyalgia rheumatica. Arthritis Care & Research. 2007;57(5):803-9.
15. Harris E, Tiganescu A, Tubeuf S, Mackie SL. The prediction and monitoring of toxicity associated with long-term systemic glucocorticoid therapy. Curr Rheumatol Rep. 2015;17(6):513.
16. Paskins Z, Whittle R, Sultan AA, Muller S, Blagojevic-Bucknall M, Helliwell T, et al. Risk of fracture among patients with polymyalgia rheumatica and giant cell arteritis: a population-based study. BMC Medicine. 2018;16(1):4.
17. Lai LYH, Harris E, West RM, Mackie SL. Association between glucocorticoid therapy and incidence of diabetes mellitus in polymyalgia rheumatica and giant cell arteritis: a systematic review and meta-analysis. RMD Open. 2018;4(1):e000521.
18. Wu J, Keeley A, Mallen C, Morgan AW, Pujades-Rodriguez M. Incidence of infections associated with oral glucocorticoid dose in people diagnosed with polymyalgia rheumatica or giant cell arteritis: a cohort study in England. Canadian Medical Association Journal. 2019;191(25):E680-E8.
19. Sagar R, Mackie S, W. Morgan A, Stewart P, Abbas A. Evaluating tertiary adrenal insufficiency in rheumatology patients on long-term systemic glucocorticoid treatment. Clinical Endocrinology. 2021;94(3):361-70.
20. Tieu J, Cheah JTL, Black RJ, Christensen R, Ghosh N, Richards P, et al. Improving benefit-harm assessment of glucocorticoid therapy incorporating the patient perspective: The OMERACT glucocorticoid core domain set. Seminars in Arthritis and Rheumatism. 2021;51(5):1139-45.
21. Vivekanantham A, Blagojevic-Bucknall M, Clarkson K, Belcher J, Mallen CD, Hider SL. How common is depression in patients with polymyalgia rheumatica? Clinical Rheumatology. 2018;37(6):1633-8.
22. Volansky R. Methotrexate mainstay: ACR guidelines reaffirm old DMARD as 'anchor drug' in RA therapy 2021 [Available from: https://www.healio.com/news/rheumatology/20210811/methotrexate-mainstay-acr-guidelines-reaffirm-old-dmard-as-anchor-drug-in-ra-therapy.

23. Ruediger C, Nguyen L, Black R, Proudman S, Hill C. Efficacy of methotrexate in polymyalgia rheumatica in routine rheumatology clinical care. Intern Med J. 2020;50(9):1067-72.
24. Caporali R, Cimmino MA, Ferraccioli G, Gerli R, Klersy C, Salvarani C, et al. Prednisone plus Methotrexate for Polymyalgia Rheumatica. Annals of Internal Medicine. 2004;141(7):493-500.
25. van der Veen MJ, Dinant HJ, van Booma-Frankfort C, van Albada-Kuipers GA, Bijlsma JW. Can methotrexate be used as a steroid sparing agent in the treatment of polymyalgia rheumatica and giant cell arteritis? Annals of the Rheumatic Diseases. 1996;55(4):218-23.
26. Ferraccioli G, Salaffi F, De Vita S, Casatta L, Bartoli E. Methotrexate in polymyalgia rheumatica: preliminary results of an open, randomized study. J Rheumatol. 1996;23(4):624-8.
27. Nazarinia Am, Moghimi j, Toussi J. Efficacy of methotrexate in patients with polymyalgia rheumatica. Koomesh journal. 2013;14(3):265-70.
28. Dejaco C, Singh YP, Perel P, Hutchings A, Camellino D, Mackie S, et al. Current evidence for therapeutic interventions and prognostic factors in polymyalgia rheumatica: a systematic literature review informing the 2015 European League Against Rheumatism/American College of Rheumatology recommendations for the management of polymyalgia rheumatica. Annals of the Rheumatic Diseases. 2015;74(10):1808-17.
29. Adizie T, Christidis D, Dharmapaliah C, Borg F, Dasgupta B. Efficacy and tolerability of leflunomide in difficult-to-treat polymyalgia rheumatica and giant cell arteritis: a case series. International Journal of Clinical Practice. 2012;66(9):906-9.
30. Diamantopoulos AP, Hetland H, Myklebust G. Leflunomide as a Corticosteroid-Sparing Agent in Giant Cell Arteritis and Polymyalgia Rheumatica: A Case Series. BioMed Research International. 2013;2013:120638.
31. Quartuccio L, Gregoraci G, Isola M, De Vita S. Retrospective analysis of the usefulness of a protocol with high-dose methotrexate in polymyalgia rheumatica: Results of a single-center cohort of 100 patients. Geriatrics & Gerontology International. 2018;18(9):1410-4.
32. Ledingham J, Gullick N, Irving K, Gorodkin R, Aris M, Burke J, et al. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. Rheumatology. 2017;56(6):865-8.
33. Mazaud C, Fardet L. Relative risk of and determinants for adverse events of methotrexate prescribed at a low dose: a systematic review and meta-analysis of randomized placebo-controlled trials. British Journal of Dermatology. 2017;177(4):978-86.
34. Solomon DH, Glynn RJ, Karlson EW, Lu F, Corrigan C, Colls J, et al. Adverse Effects of Low-Dose Methotrexate. Annals of Internal Medicine. 2020;172(6):369-80.
35. Chen S-Y, Choi C-B, Li Q, Yeh W-S, Lee Y-C, Kao AH, et al. Glucocorticoid Use in Patients With Systemic Lupus Erythematosus: Association Between Dose and Health Care Utilization and Costs. Arthritis Care & Research. 2015;67(8):1086-94.
36. Stone JH, Tuckwell K, Dimonaco S, Klearman M, Aringer M, Blockmans D, et al. Trial of Tocilizumab in Giant-Cell Arteritis. New England Journal of Medicine. 2017;377(4):317-28.
37. Clinical guide during the COVID-19 pandemic for the management of patients with musculoskeletal and rheumatic conditions who are already taking corticosteroids, or require initiation of oral/IV corticosteroids, or require an intra-articular or intra-muscular corticosteroid injection 2020 [Available from: https://www.rheumatology.org.uk/Portals/0/Documents/COVID-19/MSK_rheumatology_corticosteroid_guidance.pdf.
38. Gianfrancesco M, Hyrich KL, Al-Adely S, Carmona L, Danila MI, Gossec L, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Annals of the Rheumatic Diseases. 2020;79(7):859-66.
39. Sattui SE, Conway R, Putman MS, Seet AM, Gianfrancesco MA, Beins K, et al. Outcomes of COVID-19 in patients with primary systemic vasculitis or polymyalgia rheumatica from the COVID-19 Global Rheumatology Alliance physician registry: a retrospective cohort study. The Lancet Rheumatology. 2021;3(12):e855-e64.
40. Nowell WB, Karis E, Gavigan K, Stradford L, Zhao H, Chen L, et al. Patient-Reported Nausea and Fatigue Related to Methotrexate: A Prospective, Self-Controlled Study in the ArthritisPower® Registry. Rheumatology and Therapy. 2022;9(1):207-21.
41. Avery KNL, Williamson PR, Gamble C, O'Connell Francischetto E, Metcalfe C, Davidson P, et al. Informing efficient randomised controlled trials: exploration of challenges in developing progression criteria for internal pilot studies. BMJ Open. 2017;7(2):e013537.
42. Herbert E, Julious SA, Goodacre S. Progression criteria in trials with an internal pilot: an audit of publicly funded randomised controlled trials. Trials. 2019;20(1):493.
43. Drug information Methotrexate. https://www.versusarthritis.org/; 2021.

44. Abhishek A, Boyton RJ, Peckham N, McKnight Á, Coates LC, Bluett J, et al. Effect of a 2-week interruption in methotrexate treatment versus continued treatment on COVID-19 booster vaccine immunity in adults with inflammatory conditions (VROOM study): a randomised, open label, superiority trial. The Lancet Respiratory Medicine. 2022;10(9):840-50.
45. COVID-19 Guidance: British Soceity for Rheumatology; 2022 [Available from: https://www.rheumatology.org.uk/practice-quality/covid-19-guidance.
46. Hoekstra M, Haagsma C, Neef C, Proost J, Knuif A, van de Laar M. Splitting high-dose oral methotrexate improves bioavailability: a pharmacokinetic study in patients with rheumatoid arthritis. J Rheumatol. 2006;33(3):481-5.
47. Sherbini AA, Sharma SD, Gwinnutt JM, Hyrich KL, Verstappen SMM. Prevalence and predictors of adverse events with methotrexate mono- and combination-therapy for rheumatoid arthritis: a systematic review. Rheumatology (Oxford). 2021;60(9):4001-17.
48. Malaviya AN. Methotrexate intolerance in the treatment of rheumatoid arthritis (RA): effect of adding caffeine to the management regimen. Clinical Rheumatology. 2017;36(2):279-85.
49. Darabian S, Wade JP, Kur J, Wade SD, Sayre EC, Badii M. Using FibroScan to Assess for the Development of Liver Fibrosis in Patients With Arthritis on Methotrexate: A Single-center Experience. J Rheumatol. 2022;49(6):558-65.
50. Breedveld FC, Dayer JM. Leflunomide: mode of action in the treatment of rheumatoid arthritis. Ann Rheum Dis. 2000;59(11):841-9.
51. Flint J, Panchal S, Hurrell A, van de Venne M, Gayed M, Schreiber K, et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology (Oxford). 2016;55(9):1693-7.
52. Leeb BF, Bird HA, Nesher G, Andel I, Hueber W, Logar D, et al. EULAR response criteria for polymyalgia rheumatica: results of an initiative of the European Collaborating Polymyalgia Rheumatica Group (subcommittee of ESCISIT). Ann Rheum Dis. 2003;62(12):1189-94.
53. Russell MD, Dey M, Flint J, Davie P, Allen A, Crossley A, et al. British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids. Rheumatology (Oxford). 2022.
54. Sammaritano LR, Bermas BL, Chakravarty EE, Chambers C, Clowse MEB, Lockshin MD, et al. 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases. Arthritis Rheumatol. 2020;72(4):529-56.
55. NICE. NICE Process and Methods Guides : Guide to the Methods of Technology Appraisal 2013. London: National Institute for Health and Care Excellence (NICE); 2013 4 April 2013.
56. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. BMJ. 2013;346:f1049.
57. Philips Z, Bojke L, Sculpher M, Claxton K, Golder S. Good practice guidelines for decision-analytic modelling in health technology assessment: a review and consolidation of quality assessment. Pharmacoeconomics. 2006;24(4):355-71.
58. Monks T, Currie CSM, Onggo BS, Robinson S, Kunc M, Taylor SJE. Strengthening the reporting of empirical simulation studies: Introducing the STRESS guidelines. Journal of Simulation. 2019;13(1):55-67.
59. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ. 2002;21(2):271-92.
60. Caro JM, J. Karnon, J.Stahl, J. Ishak, J. . Discrete Event Simulation for Health Technology Assessment (1st ed.): CRC Press; 2015.
61. Karnon J, Stahl J, Brennan A, Caro JJ, Mar J, Moller J, et al. Modeling using discrete event simulation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--4. Value Health. 2012;15(6):821-7.
62. Ireland A, Wiklund I, Dale P, Hsieh R, Rourke E. Reproducibility of an asthma symptoms and rescue medication diary: Paper and AM3™ modes. European Respiratory Journal. 2011;38(Suppl 55):p4167.
63. Wagner GJ. Predictors of antiretroviral adherence as measured by self-report, electronic monitoring, and medication diaries. AIDS Patient Care STDS. 2002;16(12):599-608.
64. Twohig H, Jones G, Mackie S, Mallen C, Mitchell C. Assessment of the face validity, feasibility and utility of a patient-completed questionnaire for polymyalgia rheumatica: a postal survey using the QQ-10 questionnaire. Pilot Feasibility Stud. 2018;4:7.
65. Twohig H, Mitchell C, Mallen C, Muller S. Development and psychometric evaluation of the PMR-Impact Scale: a new patient reported outcome measure for polymyalgia rheumatica. Rheumatology (Oxford). 2022.
66. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15(5):708-15.

67. Miloslavsky EM, Naden RP, Bijlsma JW, Brogan PA, Brown ES, Brunetta P, et al. Development of a Glucocorticoid Toxicity Index (GTI) using multicriteria decision analysis. Ann Rheum Dis. 2017;76(3):543-6.
68. Lai L. Risk of diabetes mellitus associated with use of oral glucocorticoids in patients with polymyalgia rheumatica and giant cell arteritis: University of Leeds; 2020.
69. van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. Rheumatology (Oxford). 2000;39(12):1383-9.
70. Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Dore C, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA. 2017;318(23):2337-43.
71. Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. Int J Surg. 2012;10(1):28-55.
72. Riley RD, Snell KI, Ensor J, Burke DL, Harrell FE, Jr., Moons KG, et al. Minimum sample size for developing a multivariable prediction model: PART II - binary and time-to-event outcomes. Stat Med. 2019;38(7):1276-96.