CLINICAL TRIAL PROTOCOL

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

Version 3.0
07 May 2025

Short title:	Methotrexate Oral Or SubcutanEous for RA
Acronym:	MOOSE
ISRCTN:	14403521
CTA reference:	CTA 03057/0078/001-0001
IRAS Project ID:	1006576
Trial Sponsor:	University of Nottingham
Sponsor reference:	23006
Funding Source:	National Institute for Health and Care Research, Health Technology Assessment

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1 SYNOPSIS

Title	Multi-centre randomised open-label assessor-blinded two arm parallel group trial of subcutaneous versus oral methotrexate for rheumatoid arthritis (RA) with internal feasibility assessment, economic evaluation and qualitative study.
Acronym	MOOSE
Short title	Methotrexate Oral Or SubcutanEous for RA (MOOSE)
Chief Investigator	Professor Abhishek Abhishek
Objectives	**1.1 Primary:** To assess the effectiveness of a treat-to-target protocol using first line subcutaneous methotrexate on remission assessed at 24 weeks. **1.2 Secondary:** The secondary objectives are: • To assess the effectiveness of a treat-to-target protocol using first line subcutaneous methotrexate in comparison to oral methotrexate on disease activity, quality of life, mental health, employment • To compare the cost effectiveness of subcutaneous methotrexate and oral methotrexate • To compare the progression to other disease modifying anti-rheumatic drugs including biologics in those randomised to oral and subcutaneous methotrexate • To assess the acceptability of first line subcutaneous and oral methotrexate in a treat-to-target protocol
Trial Configuration	Two-arm assessor-blinded parallel group randomised controlled trial.
Setting	Secondary Care – 30 NHS hospital rheumatology clinics
Sample size estimate	386 participants will allow detection of an absolute difference of 17.5% in the proportion of participants showing remission 24 weeks after randomisation, with 90% power, and a 5% significance level (2-sided). This assumes 30% of participants in the oral methotrexate arm show remission, and that 10% of participants are lost to follow up.
Number of participants	386 participants (193 in each treatment arm)
Eligibility criteria	**Inclusion Criteria:** • Age ≥18 years • Meets American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA

	• Active RA defined as at-least one swollen joint • Willing to initiate methotrexate • DAS-28-CRP ≥2.6 **Exclusion criteria:** • RA previously treated with methotrexate or other disease modifying anti-rheumatic drugs. Patients treated with hydroxychloroquine for palindromic RA or autoantibody positive arthralgia are eligible. • Psoriasis or other immune-mediated inflammatory conditions such as inflammatory bowel disease, ankylosing spondylitis, systemic lupus erythematosus, polymyalgia rheumatica or giant cell arteritis etc. • Dementia, severe psychological disturbance i.e. mental health illness that makes receiving trial information and initial screening questions a stressful experience. • Unable to give informed consent or comply with study procedures. • Cancer treatment i.e. surgery, radiotherapy, immunotherapy or chemotherapy, currently or in the last 12 months; (current or past non-metastatic melanoma and skin cancer are eligible). • Solid organ transplant on long term daily prednisolone and/or other systemic immunosuppressive treatments • Stage 4/5 Chronic Kidney Disease (CKD), chronic liver disease (e.g. autoimmune hepatitis, primary sclerosing cholangitis, hepatitis B or C, cirrhosis etc.) • Low-dose methotrexate contraindicated • Pregnant or breast feeding • Planning to become pregnant or breast feed within the next 18 months • For men, intending to start a family in the next 18 months • Life expectancy less than 12 months
Description of interventions	**Intervention:** Subcutaneous methotrexate with 4-weekly dose escalation. **Comparator:** Oral methotrexate with 4-weekly dose escalation.
Duration of trial	The recruitment period for the trial is scheduled for 24 months. The treatment period (from randomisation to end of follow-up) is 52 weeks (approximately 12 months). The overall trial duration is 52 months starting 01 September 2022.
Randomisation and blinding	Eligible patients who consent will be individually randomised on a 1:1 allocation ratio. Patients will be randomly assigned to a treatment arm, minimised by trial centre, 28-joint disease activity score with CRP (DAS-28-CRP), and disease duration. Interventions will be prescribed open-label. Participants and their clinicians will be aware of treatment allocated. Follow-up assessors will be blinded to allocation throughout the trial.

Outcome measures	**Primary endpoint** Remission of RA, defined as DAS-28-CRP <2.6 at week 24. **Secondary endpoint** • Remission of RA at 12, and 52 weeks as defined above. • Remission of RA at 12, 24 and 52 weeks as per 2022 Boolean ACR/EULAR definition, Simplified Disease Activity Index and Clinical Disease Activity Index. • Disease activity at 12, 24 and 52 weeks measured using Clinical Disease Activity Index, Simplified Disease Activity Index and components of these scores. • Response to treatment at 12, 24 and 52 weeks using DAS-28-CRP; EULAR and, ACR 20, 50, 70 responses. • Function at 12, 24 and 52 weeks • Quality of life, fatigue, anxiety, depression at 24, and 52 weeks. • Work productivity and employment at 24 and 52 weeks. • Treatment acceptability- quantitative at 4, 24 and 52 weeks; qualitative during 4-8 and 24-32 weeks.
Statistical methods	The analysis and presentation of the trial results will be in accordance with the CONSORT guidelines and a full Statistical Analysis Plan (SAP) will be developed prior to database lock. The primary objective of the trial is to determine the effectiveness of first line subcutaneous versus oral methotrexate and as such, the principal approach to our primary comparative analysis will be to analyse as randomised without imputation of missing data, with due emphasis being placed on the confidence intervals for the between arm comparisons. Sensitivity and secondary analyses will be considered supportive to the primary.
Qualitative methods	Qualitative data collection will involve semi-structured interviews in both arms. Maximum variance sampling will ensure patient diversity e.g. age, gender, ethnicity, health literacy, perceptions of acceptability. We aim to interview approximately 10 participants in each arm, depending on data saturation. All those interviewed at 4-8 weeks will be invited to another interview between 24-32 weeks. Interviews will be transcribed verbatim and analysed thematically using a framework approach and inductive and deductive coding. For longitudinal analysis, summaries of each participant's data will be used to identify perceptions of changes in acceptability of interventions and influences of change within case (each person) and in each intervention group (cross-case).
Health economic methods	Outcome/resource use/analysis: Data on healthcare utilisation will be collected. Cost-estimates will be taken from standard literature sources, such as the British National Formulary or NHS Reference Costs. The costs of adverse events will be chosen following targeted literature reviews, as will any impact on health. Two sets of modelling will be undertaken. The first model will be restricted to the duration of the trial so that only the observed outcomes contribute directly to the estimate of cost effectiveness. The second model explicitly acknowledges that there may be benefits (and cost offsets, in particular those associated with

	increased biologic disease modifying antirheumatic drugs and potentially joint surgery) accrued beyond the duration of the trial associated with subcutaneous methotrexate use. Modelling techniques will be used to extrapolate into the future to provide estimates of cost effectiveness over longer periods of time, Comprehensive scenario / sensitivity analyses will be undertaken to explore the robustness of the results to changes in the values of key parameters to alternative plausible values, and by the inclusion of monetised values for absenteeism and presenteeism.

Amendment number	Protocol version number	Type of amendment	Summary of amendment
SA02	2.0	Substantial protocol changes submitted as part of SA02	1. The SWAT primary outcome has been amended from the proportion of participants recruited to the proportion of patients consented, as a more accurate reflection of the effect of watching a trial video on the patient's willingness to join the study. Using the proportion randomised would only include those consenting who were eligible to take part – eligibility being assumed to be independent of consent. The conversion from approach to randomised will be examined as a secondary outcome. Since it is expected that there will be large variability in conversation rates from approached to consented, due to difference practices at sites and variations in the quality of screening log completion, the threshold for switching to the PIS which shows the greater conversion rate will be decided when using blinded trial data as a basis and documented in the SWAT SAP. 2. Steroid changed to corticosteroid for greater specificity/accuracy. 3. Sub-group analyses amended to be in line with the subgroup stratification at randomisation. 4. Drug commercial name removed as the IMP is defined by its active substance only, all authorised brands in the UK may be used. 5. Additional clarification of who should help with questionnaire completion at the clinic visits. 6. Additional information to the baseline visit section to allow subcutaneous methotrexate counselling to be given at the same time as oral methotrexate counselling. This allow full disclosure of both treatment arms prior to the patient being randomised and allows sites greater flexibility with the booking of staff time for methotrexate counselling. 7. Prescription guidance to clarify that prescription can be issued by primary care via shared care agreement. 8. Change of sponsor contact name 9. Eligibility criteria has been amended to clarify that current cancer treatment is an exclusion as well as treatment in the last 12 months. 10. In the follow-up section, there has been extra clarification to the timing of dose escalation visits, to ensure all sites are working to escalate participants in accordance with the NICE guidelines.
SA04	3.0	Substantial protocol changes submitted as part of SA04	1. Clarification in section 7.2 baseline, CRP must be taken at baseline. CRP at baseline is in the data collection schedule outlined in table 4, as a research activity. The amendment to section 7.2 adds extra clarity for research sites, that screening CRP is used for eligibility/randomisation and a CRP test should also be taken at the baseline visit. 2. Systemic lupus erythematosus added to exclusion criteria for clarity.

			3. 6 months post treatment contraception for men has reduced to 3 months, in line with SmPC updates 4. Outcome S5 Blood test results will be collected using medical records, for leucocyte count, neutrophil count, platelet count, ALT, AST, creatinine, and MCV, and categorised according to CTCAE. The blood tests are collected as part of standard care, and collection and recording of blood tests in terms of safety is already outlined in section 11.1. This amendment specifies that the safety data collected will be used for outcome S5. 5. Section 6.4, update to extend recruitment for an extra 2 months, giving a total recruitment period of 24 months. Previous recruitment projection table in appendix 2 has been removed. 6. Removal of cost effectiveness analysis from the outcome list. This has been undertaken because this cannot be observed as an outcome but instead is estimated from the synthesis of other listed outcomes in order to estimate the expected incremental health gains (expressed as QALYs) and expected incremental costs. Cost-effectiveness will be generated from incremental costs and QALYs. Additionally, extrapolation of QALYs and costs beyond the study period, for instance if there is a long-term morbidity or cost implication, would not be able to be observed within the study.

2 ABBREVIATIONS

ACR	American College of Rheumatology
ADR	Adverse Drug Reaction
AE	Adverse Event
BMQ	Beliefs about Medicine Questionnaire
CDAI	Clinical Disease Activity Index
CI	Chief Investigator
CKD	Chronic Kidney Disease
CRF	Case Report Form
CRP	C-reactive Protein
DAP	Data Analysis Plan
DAS-28-CRP	Disease Activity Score 28-joints including C reactive protein
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EOT	End of Trial
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy - Fatigue
GAD-7	Generalised Anxiety Disorder Assessment
GCP	Good Clinical Practice
GH	Global Health
HAQ-DI	Health Assessment Questionnaire Disability Index
HRA	Health Research Authority
HTA	Health Technology Assessment
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
MHRA	Medicines and Healthcare products Regulatory Agency
NCTU	Nottingham Clinical Trials Unit
NHS	National Health Service
NICE	National Institute of Health Care Excellence
NIHR	National Institute of Health Research
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PGA	Patient Global Assessment
PhGA	Physician Global Assessment
PHQ-8	Patient Health Questionnaire Depression Scale
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
RA	Rheumatoid Arthritis
RA-QoL	Rheumatoid Arthritis Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development department
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDAI	Simple Disease Activity Index
SJC	Swollen Joint Count
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TFAQ	Theoretical Framework of Acceptability Questionnaire

TJC	Tender Joint Count
TMG	Trial Management Group
TSC	Trial Steering Committee
WPAI-RA	Work Productivity and Activity Impairment questionnaire – Rheumatoid Arthritis

The term ‘patient’ is used before the individual is recruited into the trial. The term ‘participant’ is used from then onwards.

TABLE OF CONTENTS

3 TRIAL / STUDY BACKGROUND INFORMATION AND RATIONALE

Rheumatoid arthritis (RA) is an inflammatory disease which most commonly affects the small joints of the hands and feet, causing considerable pain and functional impairment. It is a systemic disease and so can affect the whole body, including the heart, lungs and eyes, causing a wide range of complications for people with the disease, their carers, the NHS and society in general. RA affects 0.7% of adults in the UK and causes permanent joint damage and disability if not treated aggressively [1, 2]

Methotrexate has emerged as the first line disease modifying anti-rheumatic drug due to its safety and efficacy and is the cornerstone of modern management of RA [3]. It is usually prescribed in the tablet form, with subcutaneous injections prescribed if there is gastrointestinal intolerance or suboptimal efficacy. A minority of clinicians (14% according to our June 2020 survey of 33 UK rheumatologists) offer methotrexate injections as the first line treatment of RA in preference to oral methotrexate. However, this practice is not supported by evidence. In addition, as methotrexate injections can be painful and cumbersome, and are more expensive than tablets (£16.06 vs. £0.75 for the 20 mg weekly dose), high quality information on effectiveness, tolerability, and cost effectiveness is required before it is recommended as the first line treatment of RA.

A systematic review published in 2019 identified four randomised controlled trials (RCT) (N=703) suggesting subcutaneous methotrexate may be more effective than the oral form, with three-fold higher odds for achieving a 20% improvement in disease activity using the American College of Rheumatology (ACR) response criteria [4-7]. Another large propensity score matched cohort study from Canada also reported better control of disease activity with subcutaneous methotrexate compared to oral therapy in RA patients [8]. This is supported by a pharmacokinetic study reporting a plateau in bioavailability of oral methotrexate at doses >15 mg/week, unlike for subcutaneous methotrexate [9]. However, further high-quality studies are needed before subcutaneous methotrexate can be adopted as the first line treatment for RA. This is because existing RCTs have used a moderate fixed-dose of methotrexate e.g. 15 mg/week, and did not employ the disease activity-driven treat-to-target strategy with dose escalation and addition of other drugs as recommended in the NICE guidelines [4, 5].

In addition to this, the above-mentioned Canadian cohort study had a substantial imbalance in the starting dose of methotrexate with 87% participants prescribed subcutaneous methotrexate starting on 20-25 mg/week whereas only 41% participants commenced oral treatment at these doses [8]. Thus, participants receiving subcutaneous methotrexate may have had an undue advantage due to early high dose therapy. The results of this study from Canada also cannot be generalised to the UK as our usual clinical practice is to start on methotrexate 10-15 mg/week and escalate to 20-25 mg/week to minimise early intolerance and side-effects such as acute liver injury or cytopenia. Finally, cost effectiveness and acceptability were not evaluated in these studies.

The proportion of RA patients treated with methotrexate has increased over time [3]. Thus, whether to use subcutaneous or oral methotrexate first line is an important question for many patients and their clinicians. Moreover, if subcutaneous methotrexate increases remission rates, improves quality of life, further savings could be made through reduced use of biologic agents, fewer days off work, and reduced sickness incapacity costs. However, there are associated increased drug costs from using subcutaneous methotrexate first line and a cost

effectiveness analysis is needed before it can be recommended first line for all adults with RA.

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

4 DETAILS OF INVESTIGATIONAL MEDICINAL PRODUCT(S)

Participants will be randomised to either subcutaneous or oral methotrexate, both prescribed within their licensed use. The initial dose of methotrexate (typically 7.5-15 mg/week) will be determined by the rheumatologist prior to randomisation and will depend on the prescribing preference of the rheumatologists, taking into consideration the patient's comorbidities. Rheumatologists will be able to choose a higher or lower starting dose of methotrexate as clinically indicated and as per their usual practice.

Participants will start methotrexate and typically be reviewed 4 weekly, for 2-3 months, where their methotrexate dose may be escalated. More rapid methotrexate dose escalation e.g. up to fortnightly will be allowed if this is a clinicians' usual practice. Decisions on dose escalation will typically be guided by DAS-28-CRP and patient preference in addition to the usual care safety blood-tests. The treatment period is 52 weeks (from randomisation to end of follow-up).

4.1 Description

The IMP for MOOSE, methotrexate, is to be defined by its active substance only, in which case all authorised brands in the UK may be used.

Subcutaneous methotrexate
The typical initial dose is 7.5 mg -15 mg of methotrexate once weekly, administered subcutaneously. Rheumatologists will be able to choose a higher or lower starting dose of methotrexate as clinically indicated and as per their usual practice. Depending on the individual activity of the disease and tolerability by the patient, the initial dose may be increased gradually. A weekly dose of 25 mg is not to be exceeded.

Oral methotrexate
Oral methotrexate is the first-line NHS treatment for RA in the UK. The typical initial dose is 7.5 mg – 15 mg of methotrexate once weekly, administered orally. Rheumatologists will be able to choose a higher or lower starting dose of methotrexate as clinically indicated and as per their usual practice. Depending on the individual activity of the disease and tolerability by the patient, the initial dose may be increased gradually. A weekly dose of 25 mg is not to be exceeded.

4.2 Manufacture

Subcutaneous Methotrexate Formulation: methotrexate solution in pre-filled pen or pre-filled syringe form.

Metoject, and Zlatal have been selected out of the most commonly prescribed medications treatments to be used in this protocol as examples. Metoject is a solution for injection pre-filled injector pen, and Zlatal is a solution for injection in a pre-filled syringe. All available brands of subcutaneous methotrexate pre-filled injector pens and pre-filled syringes can be prescribed .

Metoject - medac Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6, 22880 Wedel, Germany.
UK licence number PL 11587/0076-0085

Zlatal - Nordic Group B.V., Siriusdreef 41, 2132 WT Hoofddorp, The Netherlands.
UK licence number PL 40621/0012

Oral Methotrexate Formulation: methotrexate in tablet form.

Maxtrex has been selected out of the most commonly prescribed treatments to be used in this protocol as an example. All available brands of oral tablet methotrexate can be prescribed.

Maxtrex - Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ, United Kingdom.
PL 00057/1010

4.3 Known Side effects

Common side effects of methotrexate include:

- Nausea, loss of appetite, vomiting, diarrhoea
- Mouth ulcers, skin rash
- Effects on blood tests for liver function, white blood cell and platelet numbers
- Headaches
- Mild hair loss

Full details of side effects are available in the SmPC patient information leaflet.

4.4 Reference Safety Information:

The IMP for MOOSE is to be defined by its active substance only, in which case all authorised brands in the UK may be used. Reference safety information is listed in section 4.8 of the relevant subcutaneous or oral methotrexate SmPC listed below. Other brands and doses up to 25mg may be prescribed. (Revision dates taken from section 10 of the SmPC)

Metoject PEN 7.5 mg solution for injection in pre-filled pen SmPC date of last revision 25 Mar 2022, will act as the reference safety information for subcutaneous methotrexate pre-filled pen injectors.

Zlatal 7.5 mg solution for injection in pre-filled syringe SmPC date of last revision 07 Feb 2022, will act as the reference safety information for subcutaneous methotrexate solution in pre-filled syringes.

Maxtrex 2.5 mg Tablets SmPC date of last revision 15 Mar 2022 will act as the reference safety information for oral methotrexate tablets.

4.5 Packaging and labelling

The Investigational Medicinal Product (IMP)s, have marketing authorisation and will be used in accordance with their authorisation. Therefore, labelling and packaging details are not required as standard pharmacy/clinic supplies will be used.

The allocated IMP will be dispensed to a trial participant in accordance with a prescription given by an authorised healthcare professional and labelled in accordance with the requirements of Schedule 5 to the Medicines for Human Use (SI 1994/31 94) (Marketing Authorisations etc.) Regulations 1994 that apply in relation to relevant dispensed medicinal products.

4.6 Storage, dispensing and return

All medicines are open label and prescribed within their licensed use. There are no trial-specific accountability requirements; the first prescription of both oral and subcutaneous methotrexate will be dispensed from the hospital (pharmacy or trials pharmacy) or community pharmacy depending on local policies and service configurations. Such pharmacies will follow their own local procedures for recording treatments dispensed. Usual NHS routes of prescription and drug supply will be utilised after this, and may include prescriptions issued by primary care via shared care agreements [10].

Participants should store and dispose of their allocated IMP according to the instructions in the patient information leaflet. Participants may return unused trial medication to their hospital or local pharmacy (where the medicines were dispensed). There are no additional trial specific requirements for medication disposal outside of usual practice.

5 TRIAL / STUDY OBJECTIVES AND PURPOSE

5.1 PURPOSE

To evaluate the clinical and cost-effectiveness of subcutaneous methotrexate in comparison to first line treatment with oral methotrexate in RA.

5.2 PRIMARY OBJECTIVE

To assess the effectiveness of a treat-to-target protocol using first line subcutaneous methotrexate in comparison to oral methotrexate on remission at 24 weeks.

5.3 SECONDARY OBJECTIVES

The secondary objectives are:

- To assess the effectiveness of a treat-to-target protocol using first line subcutaneous methotrexate in comparison to oral methotrexate on disease activity, quality of life, mental health, employment
- To compare the cost effectiveness of subcutaneous methotrexate and oral methotrexate
- To compare the progression to other disease modifying anti-rheumatic drugs including biologics in those randomised to oral and subcutaneous methotrexate
- To assess the acceptability of first line subcutaneous and oral methotrexate in a treat-to-target protocol

5.4 INTERNAL PILOT

An internal pilot phase has been built into the trial to allow a feasibility assessment which will examine recruitment and retention. The stop-go criteria (shown in Table 1 below) will be used to determine the progression of the trial recruitment 9 and 15 months after the first participant is randomised (unless agreed otherwise with the funder).

Recruitment will be assessed against the overall recruitment target at 9 and 15 months (recruitment projections shown in appendix 2). Retention will be reviewed at 15 months and a decision made based on the proportion of participants who have withdrawn from the trial (trial follow-up not allocated treatment) at or before the 24 week follow up visit.

Table 1: Recruitment and retention progression guidance for internal pilot

	Red	Amber	Green
% target recruitment	<50%	50-99%	≥100%
number recruited: 9 months	<40	40 - 78	79
number recruited: 15 months	<110	110 - 219	220
% withdrawn by 24 weeks*	>30%	11-29%	=<10%
Action	Stop – Following discussions with TSC and funder	Review with funder / action needed	Continue – no action needed

*15 months only

The above criteria to aid decision making about progression of the trial has been proposed by the trial team and agreed with the Trial Management Group (TMG), and funder (NIHR). The final agreement on whether the trial should stop or continue will take place after discussion with NIHR HTA.

The TMG, TSC and DMC will meet to assess trial progress against these criteria at 9 and 15 months from randomisation of the first participant. The TSC will make a recommendation to the funder at each of these points, about trial progression.

Adherence to methotrexate route of administration will not form part of the progression criteria for the trial since this is a pragmatic treat to target protocol but will be regularly monitored by the TMG. See section “7.9 Adherence” for details on how adherence will be measured.

6 TRIAL DESIGN

6.1 TRIAL CONFIGURATION

MOOSE is a pragmatic, prospective, assessor-blinded, randomised controlled superiority trial of subcutaneous methotrexate compared with oral methotrexate for RA.

Within the trial is an embedded and theoretically informed mixed-methods study to investigate the acceptability of subcutaneous and oral methotrexate. Quantitative and qualitative acceptably data will be collected at the same time as trial data [11]. Theoretical framework of acceptability and the complementary perceptions and practicalities approach will be used as a conceptual backdrop [12, 13].

The primary outcome for the trial is assessed at **week 24**, within a 52 week treatment period (from randomisation to end of follow-up) for each randomised participant. Participants wishing to stop or change their allocated treatment will be free to do so at any time point and with guidance of their rheumatologist, with any changes recorded. All participants, whether continuing with allocated treatment or not, will be followed up for 52 weeks unless they withdraw consent.

Primary endpoint

Remission of RA, defined as DAS-28-CRP <2.6 at week 24 (PE1).

Table 2. Secondary endpoint

Further details on each of the following outcomes can be found in Appendix 1.

	Outcome	Timepoints
E1	Remission of RA (DAS-28-CRP)	12, 52 weeks
E2	Remission of RA (SDAI)	12, 24, 52 weeks
E3	Remission of RA (CDAI)	12, 24, 52 weeks
E4	Remission of RA (ACR/EULAR 2022 Boolean)	12, 24, 52 weeks
E5	Disease Activity of RA (CDAI)[1]	12, 24, 52 weeks
E6	Disease Activity of RA (SDAI)[1]	12, 24, 52 weeks
E7	Response to treatment (ACR20, ACR50, ACR70)	12, 24, 52 weeks
E8	Response to treatment (EULAR response criteria)	12, 24, 52 weeks
E9	DAS-28-CRP score	12, 24, 52 weeks
E10	SDAI score	12, 24, 52 weeks
E11	CDAI score	12, 24, 52 weeks
E12	Swollen joint count	12, 24, 52 weeks
E13	Tender joint count	12, 24, 52 weeks
E14	Patient global assessment (CDAI, SDAI question) (PGA)	4, 8, 12, 24, 52 weeks
E15	Physician global assessment (PhGA)	12, 24, 52 weeks
E16	Patient global health (ACR question) (PGH)	12, 24, 52 weeks
E17	CRP	12, 24, 52 weeks
E18	Patient pain	12, 24, 52 weeks
E19	Function (HAQ-DI)	12, 24, 52 weeks
E20	Fatigue (FACIT-F)	24, 52 weeks
E21	Anxiety (GAD-7)	24, 52 weeks
E22	Depression (PHQ-8)	24, 52 weeks
E23	Treatment acceptability (TFA)	4, 24, 52 weeks
E24	Beliefs about Medicines (BMQ)	4, 24, 52 weeks
E25	EQ-5D-5L	12, 24, 52 weeks
E26	Quality of life (RA-QoL)	24, 52 weeks
E27	Work productivity and employment (WPAI)	24, 52 weeks
E28	Proportion of participants receiving corticosteroid(s)	12, 24, 52 weeks

E29	Proportion of participants who discontinue randomised treatment	12, 24, 52 weeks
E30	Time to discontinuation of randomised treatment	By 52 weeks
E31	Proportion of participants starting on any additional/alternative DMARDs	12, 24, 52 weeks
E32	Time to start on any additional/alternative DMARDs	By 52 weeks
E33	Proportion of participants starting a biologic drug	12, 24, 52 weeks
E34	Time to start of biologic drug	By 52 weeks
	Qualitative outcomes	
Q1	Treatment acceptability (interviews)	4-8 weeks, 24-32 weeks
	Safety outcomes	
S1	Incidence of infection	4, 8, 12, 24, 52 weeks
S2	Incidence and severity of methotrexate side effects	4, 8, 12, 24, 52 weeks
S3	Incidence, type and severity of AEs	12, 24, 52 weeks
S4	Incidence of SAEs	52 weeks
S5	Bloods	12, 24, 52 weeks

[1]As remission, low, moderate, or high disease activity6.1.3 Safety endpoints

The incidence of the following infections will be collected at 4, 8, 12, 24 and 52 weeks

- Herpes Zoster (Shingles)
- Urinary tract infection requiring antibiotics
- Chest infection or pneumonia requiring antibiotics
- Skin or soft tissue infection (also called cellulitis) requiring antibiotics
- COVID-19 (must have had a positive PCR or lateral flow test)

The following methotrexate side effects will be collected at 4, 8, 12, 24 and 52 weeks:

- Nausea
- Abdominal Pain
- Bloating of the abdomen
- Diarrhoea
- Vomiting
- Mucositis (oral)
- Injection site reaction (methotrexate injection only)

The severity of these side effects based on CTC criteria will also be collected.
Additional adverse events (AEs) will be collected at each clinic visit.
Discontinuation of methotrexate due to safety or tolerability concerns will also be recorded as part of the eCRF and reviewed monthly by the Trial Management Group (TMG). The Data Monitoring Committee (DMC) will review safety and tolerability data annually, or more regularly at the request of either the TMG or DMC.

Serious adverse events will be recorded and reported within 24 hours of awareness of the event following the procedure outlined in section 11.4 Reporting of adverse events: “Reporting timelines” of this protocol.

Blood tests to screen for idiosyncratic blood, liver, or kidney damage will be taken as part of routine safety monitoring for the duration of treatment. Abnormal results relating to leucocyte

count, neutrophil count, platelet count, alanine transaminase (ALT) level, aspartate transaminase (AST) level, and creatine level will be recorded in the CRF. Additional results of concern should be reported as adverse events as per Section.

See section 7 “Trial Treatment and Regimen” for further details on the data collection timepoints.

Stopping rules and discontinuation

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected recruitment targets, for safety or any other administrative reasons. The Sponsor shall take advice from the TSC and the funder (NIHR HTA) as appropriate in making this decision.

Study Within A Trial (SWAT)

A SWAT will be embedded into the trial to investigate whether inclusion of a trial information video (available via QR code or URL) within the Participant Information Sheet (PIS) with trial information increases recruitment over a PIS without the link. Sites will be randomised to one of the following:

- Intervention Group 1: PIS with QR code to information video
- Intervention Group 2: Standard PIS

Randomisation will take place prior to the specified site’s Site Initiation Visit (SIV), using a web-based randomisation system developed and maintained by the Nottingham Clinical Trials Unit (NCTU) and hosted on a secure server, accessed via a secure website.
The video topics were suggested by our patient advisory group and will include information on what the MOOSE trial is about, a summary of what participation involves, the value of participation, and the next steps to take if considering joining the trial. There will also be a section on how to take methotrexate in subcutaneous forms. The video will be embedded in the REDCap database, to allow the number of times the video has been viewed to be recorded.

The primary outcome will be the proportion of patients given a PIS who are consented at each site.
The secondary outcomes will include the proportion of participants providing primary outcome data (at 24 weeks), and the proportion of participants remaining in the trial at 52 weeks.

It is planned that interim analyses comparing the proportions of participants consenting in the two intervention groups (those with PISs with the QR code to the information video and those with PISs which do not have the QR code) will be performed at 9 and then potentially at 15 months after the first participant is randomised to determine whether there is a greater proportion consenting in either of the intervention groups.

Where there is a notable difference in consent rates (such a difference will be defined in the SAP for the SWAT) at 9 months, the PIS which is associated with the higher consent rate will be adopted for the remainder of the trial. If there is no difference, an additional interim analysis will be performed at 15 months. If a notable difference is observed at this point, the PIS which is associated with the higher consent rate will be adopted for the remainder of the trial. If there is no notable difference observed, the trial will continue recruiting to the end using both PISs.

6.2 RANDOMISATION AND BLINDING

Eligible patients who consent will be allocated to a 1:1 ratio to receive either subcutaneous methotrexate or oral methotrexate.

Treatment will be assigned randomly using a minimisation algorithm balancing by trial recruiting centre, DAS-28-CRP (<5.1 and ≥5.1) and disease duration (<4 months, 4-12 months, and >12 months). These variables are selected due to their likely association with the primary outcome. Allocation will be concealed using a web-based randomisation system developed and maintained by the Nottingham Clinical Trials Unit (NCTU) and hosted on a secure server, accessed via a secure website.

Interventions will be prescribed open-label, patients and their rheumatologist and usual care team will know which treatment has been allocated.

Disease activity will be assessed using the DAS-28-CRP by a member of the research or usual care team (usually a nurse) blinded to the participant's treatment allocation throughout the trial. The outcome assessors will remind participants not to disclose their treatment allocation at the start of every assessment appointment.

All known instances of blinded outcome assessors being made aware of treatment will be investigated and recorded on the trial database.

Table3. Blinding status per role in trial

Role	Status	Justification
Participants	Not blinded	Interventions will be open-label therefore participants will know what treatment they are taking.
Rheumatologists	Not blinded	Interventions will be open-label therefore rheumatologists will be aware of treatment allocation.
Disease activity (DAS-28-CRP) assessors	Blinded	Outcomes, including the primary outcome, will be completed by a research or usual care team member blinded to participant allocation throughout the trial.
Principal Investigators	Not blinded	The PIs will be aware of the treatment allocation as they will need to review participant data prior to signing off the CRF.
Treatment acceptability interviewers (Qualitative researchers)	Not blinded	The researcher(s) will ask questions on participant's acceptability of allocated treatment and will have access to limited unblinded information within the database.
Trial management staff at NCTU	Not blinded	The Trial Management team will have access to participant data that may have the potential to unblind them to treatment allocation.
Data Management staff at NCTU	Not blinded	The Data Management team will have access to all database information in order to maintain the database and manage queries.
Trial statistician	Blinded	The trial statistician will have access to summary adherence to allocated treatment arm (oral or subcutaneous) provided by an independent statistician during the recruitment and follow up phase but will not have access to any individual participant data with the

Role	Status	Justification
		potential to unblind them until after database lock. Provision of any unblinded disaggregated data, e.g., for the DMC, will be carried out by an independent unblinded statistician.
Independent statistician	Not blinded	The independent statistician will provide the DMC with the unblinded treatment group data for the closed report.
Chief Investigator (CI)	Partially blinded	The CI will only have access to participant identifiable data for participants that they randomise within their site. They will not have access to other sites' participant data with the potential to unblind until after database lock. SAE causality assessment review will be undertaken blinded unless the SAE is determined to be related to trial treatment, at which point the CI will be unblinded if the SAR is assessed as not expected against at least one RSI.
TMG	Partially blinded	Except in the specified roles, noted in this table, members of the TMG will not have access to any participant data with the potential to unblind until after database lock.
DMC	Not blinded	The independent members of the DMC will be provided with data presented by treatment group in order to perform their oversight role. These data will be provided by an independent statistician.
TSC	Blinded	Except in the case of a specific recommendation from the DMC, independent members of the TSC will not have access to any participant data with the potential to unblind until after database lock.

6.2.1 Maintenance of randomisation codes and procedures for breaking code

Only researchers assessing disease activity (DAS-28-CRP) will be blinded to treatment allocation. Interventions will be open-label and both participants and research clinicians will be aware of the treatment allocation, therefore there is no requirement for blind-breaking procedures.

6.3 TRIAL MANAGEMENT

The trial is funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme. The Sponsor is the University of Nottingham. The trial will be managed and co-ordinated by the NCTU.

The Chief Investigator has overall responsibility for the trial and shall oversee all trial management. The data custodian will be the Chief Investigator.

Trial Management Group (TMG)
The TMG will meet on a regular basis (approximately monthly) and will be responsible for the day-to-day management of the trial. The full co-applicant team and NCTU staff responsible for the day-to-day management of the trial will form the TMG.

The TMG will ensure high quality trial conduct, to time and within budget, monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the integrity of trial itself. The TMG will also be responsible for ensuring project milestones are achieved.

Trial Steering Committee (TSC)
The role of the TSC is to maintain oversight of the trial, monitor progress and provide advice to the trial team. The TSC will consist of an independent chair, and other independent members with clinical and research expertise including patient representatives. The CI will also be a member of the TSC.

The TSC will operate in accordance with a trial-specific charter, the funder's guidelines and the relevant NCTU Standard Operating Procedure (SOP).

The TSC will meet at least once a year during the trial, including following completion of a 9-month and 15-month internal pilot period to review the results of the internal pilot and decide on recommendations regarding trial progression. Additional meetings may be called and the TSC may, at their discretion, request to meet more frequently.

The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee.

Data Monitoring Committee (DMC)
The role of the DMC is to give advice on whether the accumulated data from the trial, together with the results from other emerging research, justifies the continuing recruitment of participants.

Members of the DMC will be independent of the trial and have relevant clinical, statistical and other methodological experience of clinical trials.

The DMC will operate in accordance with a trial-specific charter, the funder's guidelines and the relevant NCTU Standard Operating Procedure (SOP).

The DMC will meet at least once a year during the trial, including following completion of a 9-month and 15-month internal pilot to review the results of the internal pilot and make recommendations to the TSC on trial progression. They will also be responsible for monitoring the data for consistency with the sample size assumptions and recommending, if necessary, changes to the sample size. Additional meetings may be called, and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified.

The DMC will report directly to the Chair of the TSC who will convey the findings of the DMC to the TSC, TMG and Sponsor as applicable.

6.4 DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT

Participation Duration: The treatment period is 52 weeks from randomisation to end of follow-up.

All participants, whether continuing with allocated treatment or not, will be followed up for 52 weeks from randomisation.

Optional consent will be sought for a separately funded 2-year follow-up of randomised participants. It is to be noted that 2-year follow up will not be possible if such funding cannot be secured.

Trial Duration: The trial will last 52 months.
The recruitment period will be 24 months, including the 15-month pilot period (including an initial review of recruitment at 9 months), with a 52-week follow-up/treatment period (Last Participant – Last Visit). Once follow-up of the last participant is completed, database lock, analysis and reporting will take a further six months.

6.4.1 End of the Trial

The end of the trial is defined as the date of the final database lock. NCTU will notify the MHRA and REC that the trial has ended within 90 days of the end of trial.

If the trial has terminated early, NCTU will inform the MHRA and REC within 15 days of the end of trial.

6.5 SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

Participants will be recruited from secondary care rheumatology clinics across the UK (approximately 30 sites). Potential eligible participants will be given a PIS about the trial by their usual clinical care team (which may include the investigator), typically, around the time of their first presentation to the rheumatology clinic after diagnosis of RA has been made, methotrexate is offered as a treatment, and the patient is willing to consider starting methotrexate. Patients must have been educated at this stage about the risks and benefits of treatment with methotrexate as per usual care. Patients will be provided with the trial PIS either in person to take home or posted to them following their presentation visit, to consider their participation in the trial. Each PIS will be individualised with the site logo and contact details, and the QR code/web address for the video if that site has been randomised to provide that information in the SWAT. The number of PISs given to patients will be recorded at each site. Participants will be phoned by a member of the usual clinical care team prior to their next clinic visit to answer any questions the patient may have about the trial and provide further information as needed.

If there is initial diagnostic uncertainty, patients may be approached and informed about the trial (as described above) after the results of investigations that confirm RA diagnosis become available. This could be in the form of a telephone call and/or posting of the PIS with a cover letter. Information about the trial will also be on display in the relevant clinical areas.

It will be explained to the potential participant that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained to patients prior to joining the trial, that they can withdraw at any time but that attempts may be made to avoid this occurrence. In the event of their full withdrawal from the trial, it will be explained that their data collected so far cannot be erased and we will use the data in the final analyses where appropriate. This information will be reiterated at the point of receiving the withdrawal request.

Once consented the research assessments are undertaken, and the initial dose of methotrexate (typically 7.5-15 mg/week) will be determined by the rheumatologist prior to randomisation. The participant will then be randomised to either subcutaneous or oral methotrexate and commence treatment.

More detailed information is detailed below in section 6.5.7 for informed consent and section 7.1 for screening.

Eligibility criteria

The target population for the trial is methotrexate naïve adults with active RA.

Participants will be required to meet the 2010 ACR/EULAR classification criteria for RA to allow for comparability with other research studies. Applying these criteria do not require any additional investigations above and beyond what is required for routine clinical care of patients with early inflammatory arthritis in the UK.

Inclusion criteria

- Age ≥18 years.
- Meets American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA.
- Active RA defined as at-least one swollen joint assessed by a rheumatologist.
- Willing to start treatment with oral or subcutaneous methotrexate.
- DAS-28-CRP ≥2.6 (blood test from initial clinic visit to be used to calculate this score at baseline visit).

Information on acceptable concomitant treatments and medications is included in section 7.8 Concomitant and rescue medications and treatments.

Exclusion criteria

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

- Life expectancy less than 12 months

Contraception requirements

Participants of childbearing potential
For persons of childbearing potential a highly effective method of contraception must be used during methotrexate treatment and for 6 months after stopping treatment. Acceptable contraceptive methods include: established use of the combined oral pill, injected or implanted hormonal methods; placement of an intrauterine device (IUD) or intrauterine system (IUS); true abstinence (when this is in line with the preferred and usual lifestyle of the participant); or vasectomised partner.

Male participants with partner of childbearing potential
For participants with partners of childbearing potential an effective method of contraception must be used during methotrexate treatment and for 3 months after stopping treatment. Acceptable contraceptive methods include: established use of oral, injected or implanted hormonal methods; placement of an intrauterine device (IUD) or intrauterine system (IUS); condom or occlusive cap (diaphragm or cervical/vault caps) with spermicide; true abstinence (when this is in line with the preferred and usual lifestyle of the participant); or vasectomy.

Expected duration of participant participation

Trial participants will be participating in the trial for 52 weeks (12 months) from randomisation (baseline visit).

Withdrawal of participants from therapy or assessments

Participants will be assured that they may withdraw from the trial at any time, without giving a reason and without any impact upon any treatment they are currently receiving or any prejudice towards their future care.

Participants who do not adhere to their allocated treatment are not required to withdraw, please see section 7.9.

Prior to randomisation

Any patients that request to withdraw their consent prior to randomisation will be withdrawn completely from the trial; they will not be randomised, and follow-up questionnaires will not be issued.

Post randomisation
Participants can withdraw consent to participate in the trial at their own request or at the discretion of the Investigator. Participants will be made aware that discontinuation from either treatment or follow-up will not affect their future care. Participants will be made aware (via the PIS and ICF) that should they withdraw, the data collected will be retained and may still be used in the final analysis.

Where a participant wishes to withdraw from the trial, their reason for doing so will be explored by research staff to determine whether there are ways they can remain in the trial - for example by reducing the burden of completing some follow-up questionnaires. Sites will receive training on acceptable methods to maximise retention within the trial. The right of the participant to withdraw without providing a reason does remain paramount.

Participants who withdraw after randomisation will not be replaced and all data collected up to the point of withdrawal will be used in the analysis.

Where optional consent was provided, participants can request to discontinue from the following activities without impacting their participation in the main trial follow-up:

- Receiving trial communications e.g., texts, phone calls or emails from the NCTU trial team
- Receiving trial results
- Collection of 2-year follow-up data
- Receiving information regarding the treatment acceptability interviews

Participants who become pregnant

Participants who become pregnant whilst taking methotrexate must stop taking methotrexate treatment immediately, in line with standard care. Participants can remain on the trial to complete follow-up (completing questionnaires and attending trial assessment visits) if agreed between the participant and clinical team. The occurrence of pregnancy will be captured at site via a trial pregnancy notification form. Please see section 11.5 for information on pregnancy reporting and follow-up.

Informed consent

All participants will provide written informed consent. The consent form will be signed and dated by the participant before they enter the trial. The Investigator (or delegate) will explain the details of the trial and provide a PIS at their initial visit (prior to the randomisation visit), ensuring that the participant has sufficient time to consider participating or not. The Investigator (or delegate) will answer any questions that the participant has concerning trial participation. The PIS may be posted out to potential participants by the clinical care team if RA diagnosis has not been confirmed at the time of the initial visit or if a potentially eligible patient has not been approached in clinic.

Written informed consent will be collected from each participant before they undergo any interventions, including questionnaire completion, related to the trial. One copy of the consent form will be kept by the participant, one will be kept by the Investigator and uploaded to the trial REDCap database, and a third will be retained in the participant's hospital records. Along with the completed consent form, the version number and date of the PIS provided to the participant and the date the consent was obtained should also be recorded on the participant's medical notes.

Optional consent will be sought to be contacted about participation in the treatment acceptability interviews. This will explain that we want to talk to a small number of people in the trial about their experiences and that not everyone who gives consent will be contacted.

Those who consent to contact will be sent a treatment acceptability PIS by the NCTU, with a reply slip to be returned to NCTU. The contact details of those willing to participate in the interview study will be shared with the qualitative researcher at Keele University. They will be contacted by the qualitative researcher who will explain the purpose of the interviews, and a summary of what participation will involve for those who choose to take part. If the patient expresses verbal interest to take part, the researcher will email the link to an electronic consent form which will be created in REDCap. Should a participant not complete their consent form before the interview date but are still willing to participate i.e. they answer the call for the interview and state willingness when asked by the interviewer, it will be read out by the interviewer and the participant will give their consent verbally with the researcher

completing the form on their behalf, noting that consent was taken verbally. This will be digitally audio/video-recorded, according to participant preference, and the digital file saved with the interview recordings and labelled with the participants' unique ID number.

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial or treatment acceptability interviews, continuing consent may be obtained (where the TMG deem necessary) using an amended Consent form which will be signed by the participant.

Optional consent will also be gained to share the trial results with participants at the point of publication.

Optional consent will also be sought to follow-up participants at 2 years post randomisation, if funding is obtained for a follow-up study.

7 TRIAL TREATMENT AND REGIMEN

Eligible patients will be approached during their initial presentation visit at the clinic and once randomised will be followed up as part of the trial for 52 weeks. Table 4 outlines the participant assessment and data collection schedule for the duration of their trial participation.

7.1 Screening

Eligible patients will be approached by a member of their usual care team, usually around the time of their first presentation to the rheumatology clinic. During this routine visit they will have clinical assessments, initial treatment e.g. with corticosteroids, blood tests including full blood count, liver function test, urea electrolytes and creatinine, CRP and ESR, and imaging as per usual practice. No trial specific assessments will be made at this stage, and prior to consent being gained. In accordance with standard practice, auto-antibody (Rheumatoid Factor (RF), and anti-CCP antibody), should be checked at the screening visit if not already previously checked. Similarly, inflammation markers (C-reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR)) and any safety blood tests should also be checked at the screening visit.

Patients may be approached about taking part in the MOOSE trial by a suitably delegated member of their clinical care team. This could be face-to-face at their clinic visit with a PIS provided to take home and read or in the form of a telephone call and/or posting or emailing of the PIS and a cover letter after their clinic visit.

Approximately 2 days to a week after their appointment, potentially eligible patients will be contacted by phone, by a member of the clinical care team to provide more information about the trial, answer any questions the patient may have and to ask whether they would be interested in participating in the trial.

7.2 Baseline

Patients will return to the clinic approximately two weeks after their initial visit, for routine clinical assessments and methotrexate counselling. Methotrexate counselling will be provided as per standard practice and will include importance of not becoming pregnant/fathering child, only taking the dose once a week, and what to do in the event of an overdose. Depending on

local staffing and clinic capacity, methotrexate counselling should also include guidance for taking both oral or subcutaneous methotrexate, with the health professional demonstrating the technique of using methotrexate injection, disposing of sharps, and handling any spillage. If such education about methotrexate route of administration is not possible at this stage, it should be done immediately after randomisation. Eligibility will be assessed by a medical doctor or a delegate (e.g. a nurse) who is assessed by the PI as fully qualified and competent to discuss the implications of the use of methotrexate and answer any questions from the participant, before the patient is consented to take part in the study. Where eligibility is assessed by a delegate (e.g. a nurse), it will need to be confirmed with a medical doctor. Patients of childbearing potential will be asked to take a pregnancy test during this visit, after consent has been taken, and a negative test confirmed before they continue in the trial. Eligibility will accordingly be confirmed by a medical doctor. In the absence of pregnancy effective contraception must be used for the duration of the trial and 6 months thereafter. Those who have verbally agreed to participate during their telephone call will meet with a research nurse or PI or deputy to discuss the trial, ask questions, and complete the consent form.

Following consent, but prior to randomisation patients will provide demographic details and complete clinical assessments. DAS-28-CRP scores for eligibility assessment should be calculated using joint counts, and patient global assessed at the baseline visit, and the CRP from the results of the blood tests taken during their initial presentation visit. A further baseline CRP should be obtained from blood tests taken at the baseline visit. Baseline questionnaire data will also be collected, including whether the participant watched the SWAT video if they were randomised to the PIS containing the video link. The rheumatologist will determine the initial dose of methotrexate (typically 7.5-15 mg/week), depending on their prescribing preference, and the patient's comorbidities. However, a higher or lower starting dose may be used if clinically indicated and as per the rheumatologists' usual practice.

Participants will then be randomised using a web based, concealed randomisation system to receive either subcutaneous methotrexate or oral methotrexate. For participants randomised to the subcutaneous methotrexate arm, the nurse will demonstrate the technique of using methotrexate injection, disposing sharps, and handling any spillage if not already demonstrated, or if there is need for reiteration. Both subcutaneous and oral methotrexate are taken as a single weekly dose. Patients randomised to subcutaneous methotrexate will administer the drug at home.

Both subcutaneous and oral methotrexate will be dispensed from the hospital or community pharmacy at the randomisation visit as per usual practice in that region, with folic acid, as per the British Society for Rheumatology guidelines.

7.3 Follow-up visits (Routine visits)

Dose Escalation

Dose escalation should occur in line with usual clinical practice by a suitably qualified clinician (e.g., rheumatologist, specialist nurse or pharmacist) who has been delegated the activity by the trial PI. This could be during the same visit as the DAS-28-CRP score is calculated or remotely following the assessment visit in line with the recruiting clinic's local practice, for example if they are awaiting a CRP result to measure the level of inflammation from the clinic visit. A full blood count, urea electrolytes and creatinine, liver function test must be checked 2 weeks after a dose escalation as per the British Society of Rheumatology guidelines. If a participant wishes not to escalate treatment, this decision will be respected.

Participants should have the CRP blood test on the same day as their clinic visit, or if preferred by the rheumatology team, the treating clinician can request that the blood test be take up to 2 days prior to the clinic visit.

Routine clinical visits (no research activity)

Week 4 and week 8

Participants will be reviewed in the rheumatology clinic at approximately 4 weekly intervals (flexibility of routine clinical visits allows for these visits to take place at 2-4 weeks and again at 6-8 weeks after initial treatment) as recommended in the NICE guidelines, as part of their standard care. The dose may be escalated at these visits in line with usual clinical practice. The initial dose escalation should not take place at less than 2 weeks after initial treatment. At weeks 4 and 8, participant side effects will be self-reported by postal or online questionnaire. Online questionnaires are completed by a link unique to the participant that is emailed to their validated email address. Those who opt for postal questionnaires at weeks 4 and 8 will be provided with a return envelope to the NCTU where questionnaire responses will be entered to the database by the trial team. Side effects to methotrexate will be assessed and any early intolerance will be assessed by history taking and physical examination as needed. These issues will be addressed at these appointments by the patient's usual care team as per their usual care procedures.

At week 4 participants will also be asked to complete the TFAQ, and BMQ questionnaires.

Study assessment visits

Trial assessment visits should be scheduled to take place on the specified day where possible, or within 2 days (e.g. 12 weeks +/- 2 days), where attendance on a specific date is not possible (e.g. over a weekend).

Week 12 (Combined clinic and research visit)

At week 12, a research or usual care team member, blinded to the participant's treatment allocation will make an assessment of TJC, SJC, and PhGA. Other assessments such as AE and whether participants are taking their randomised treatment as planned can be completed by an unblinded team member.

The DAS-28-CRP score will be recorded in the eCRF and patient medical notes and, if this is ≥ 2.6, the dose of methotrexate may be increased in 2.5 to 10 mg increments by the usual care team, depending on the prescribing preference of the rheumatologist (or delegate), and the participants' comorbidities. Dosage will not exceed the maximum recommended for rheumatoid arthritis treatment, of 25mg.

Participants should have the CRP blood test on the same day as their clinic visit, or if preferred by the rheumatology team, the treating clinician can request that the blood test be take up to 2 days prior to the clinic visit.

Participants will complete their global assessment, participant pain, infections and side effects, HAQ-DI, and EQ-5D-5L questionnaires during their visit to clinic, but prior to their RA assessment. If required a blinded researcher or usual care team may assist the participant in completing this questionnaire.

Week 24 (Research visit only)

Participants will attend a trial-specific visit 24 weeks post randomisation. During the visit, side effects to methotrexate will be assessed and any intolerance will be clinician assessed. A research nurse or usual care team member, blinded to the participant's treatment allocation

will make an assessment of TJC, SJC, and PhGA. If DAS-28-CRP is ≥ 2.6, the dose of methotrexate may be increased and/or alternate DMARDs prescribed, depending on the prescribing preference of the rheumatologist (or delegate), and the participants' comorbidities. Other assessments such as AE and whether participants are taking their randomised treatment as planned can be completed by an unblinded team member.
At the week 24 clinic visit, participants must have the CRP blood test on the same day as their clinic visit.

Participants will also be asked to complete the global assessment, participant pain, infections and side effects, HAQ-DI, EQ-5D-5L. RA-QoL, FACIT-F, PHQ-8, GAD-7, WPAI-RA, TFAQ, and BMQ questionnaires during their visit to clinic, but prior to RA assessment.

Week 52 (Combined clinic and research visit)
Participants will have their final review (as part of the trial) at the 52 week visit. During the visit, side effects to methotrexate will be assessed and any intolerance will be assessed. A research nurse, or usual care team member, blinded to the participant's treatment allocation will make an assessment of TJC, SJC, and PhGA. If DAS-28-CRP is ≥ 2.6, the dose of methotrexate may be increased and/or other DMARDs prescribed. Other assessments such as AE and whether participants are taking their randomised treatment as planned can be completed by an unblinded team member.
Participants should have the CRP blood test on the same day as their clinic visit, or if preferred by the rheumatology team, the treating clinician can request that the blood test be take up to 2 days prior to the clinic visit.

All blood tests, including those taken at standard care clinic visits, and those taken at research visits, will be labelled, analysed and destroyed as per the local NHS hospital policy.

Participants will be asked to complete the global assessment, participant pain, infections and side effects HAQ-DI, EQ-5D-5L. RA-QoL, FACIT-F, PHQ-8, GAD-7, WPAI-RA, TFAQ, and BMQ during their visit to clinic, but prior to RA assessment. If required a blinded researcher (at baseline visit pre-randomisation) or usual care team (at any visit) may assist the participant in completing this questionnaire.

7.4 Use of participant prompts and reminders

Participant contact details will be collected at baseline, after informed consent has been given by the participant. Strategies to minimise loss to follow-up will include email communications about trial progress, email or letter communications about follow up visits at 24 and 52 weeks, and text messages and email reminders will be sent to participants to prompt completion of the 4 and 8 week questionnaires. Participants may also be contacted by telephone by a member of the trial team in order to collect follow up data (if no responses are received).

7.5 Treatment acceptability interviews

Semi -structured interviews will be conducted to provide enhanced understanding of treatment acceptability and adherence to allocated treatment over time. Information on the interviews will be provided during the initial trial discussion and patient participant information sheet. A sample of those who choose to consent to be contacted (optional consent item) will be invited to participate and given an interview specific information sheet, outlining the structure and frequency of the interviews. Interviews will be conducted during weeks 4-8 and research weeks 24-32 and will be conducted remotely by phone or Microsoft Teams, with video or audio recording, according to participant preference. Teams interviews and phone calls will be video or audio recorded, and a written copy will be made by a professional

transcription company. All those interviewed at 4-8 weeks will be invited to another interview between 24-32 weeks.

7.6 Two year follow-up

Additional funding will be sought for data collection at 2-years for trial participants. Data on the DAS-28-CRP measured as part of usual care closest to the 2-year follow-up and progression to other DMARDs including biologics will be collected. Sites will be asked to enter data directly into an eCRF, following confirmation of secured funding. Participants will be asked to consent to providing 2-year follow-up data as part of their trial consent form. There will be no requirement for research visits or assessments.

7.7 Post trial care

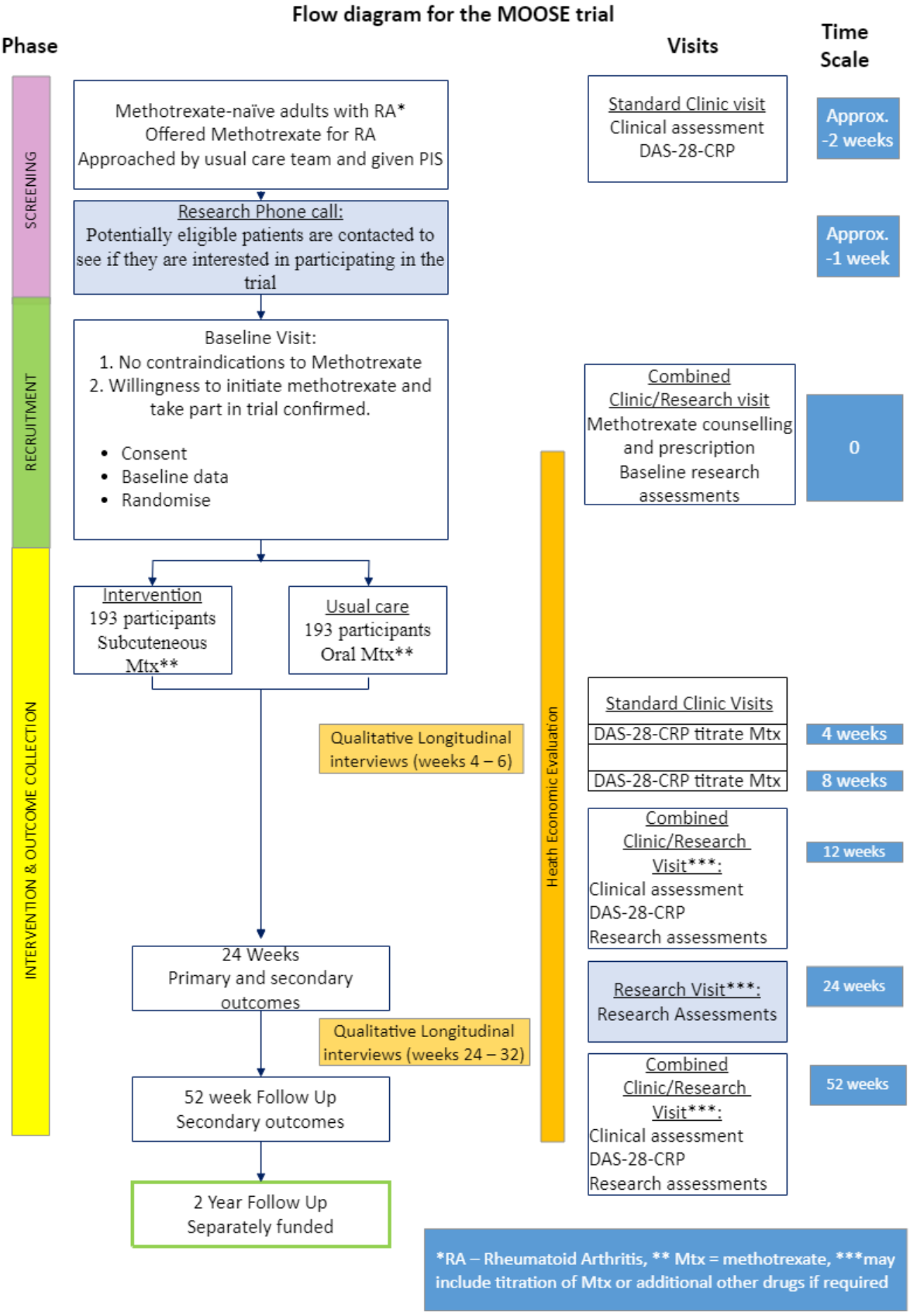
Once the participant has completed their 52 week visit, they will continue to be treated by their usual care team following local guidelines. Where both the rheumatologist (or delegate) and the participant agree, post trial treatment can continue in accordance with the participant's randomised allocation.

Table 4: Data collection schedule. Legend: X – Usual care, X – Research activity

	Screening	Baseline	Week 4	Week 8	Week 12	Week 24	Week 52
Demographic details		X					
Swollen joint count*	X	X			X	X	X
Tender joint count*	X	X			X	X	X
CRP* (blood test)	X	X			X	X	X
Patient global health*	X	X	X	X	X	X	X
Methotrexate dose, route			X	X	X	X	X
Methotrexate adherence			X	X	X	X	X
Corticosteroid dose		X			X	X	X
Other drugs incl. biologics		X			X	X	X
Side effects and infections			X	X	X	X	X
Servious adverse events			X	X	X	X	X
Physician global health*		X			X	X	X
Patient pain*		X			X	X	X
HAQ-DI*		X			X	X	X
EQ-5D-5L		X			X	X	X
RA-QoL		X				X	X
FACIT-F		X				X	X
PHQ-8, GAD-7		X				X	X
WPAI-RA		X				X	X
Health literacy		X					
BMQ			X			X	X
TFAQ			X			X	X
Longitudinal interviews			X			X	

*These measurements will be used to compute remission, DAS-28-CRP score, Clinical Disease Activity Index, Simplified Disease Activity Index, EULAR, and ACR responses.

Diagram 1: Patient pathway



7.8 Concomitant Treatments

Initial use of combination therapy (e.g. methotrexate plus hydroxychloroquine and/or sulfasalazine etc.) will not be permitted. Patients already taking hydroxychloroquine for palindromic RA or antibody positive arthralgia will be allowed to continue on hydroxychloroquine at the discretion of their rheumatologist.

Apart from the above restriction all concomitant medications will be used throughout the trial as per usual practice.

The following are examples of concomitant medications and therapy input that are permitted for use to support participants with the initial management of disease activity and management of flares in both trial groups. It should be noted that this is not an exhaustive list and the rheumatologist can use any treatment concomitantly with the exception of initial combination therapy with methotrexate and another steroid-sparing DMARD.

- Corticosteroids to control disease activity when starting on methotrexate. The dose of corticosteroids depends on disease activity, presence of comorbidities such as diabetes, and the route (oral versus intra-muscular) and on the preferences of the participant and rheumatologist. As knowledge of allocation to trial drugs may affect the dose of corticosteroids used, the rheumatologist will be required to decide on initial corticosteroid treatment regime prior to randomisation.
- Intra-articular corticosteroid injections will be allowed without any restrictions for the duration of the trial.
- Non-steroidal anti-inflammatory drugs (NSAIDs) and simple analgesics and opioid analgesics will be allowed to be used throughout the trial.
- RA flares during the trial will be treated as per rheumatologists' usual clinical practice using any of the above interventions alone or in combination.

If a participant is unwilling to increase the methotrexate dose, develops side-effects to methotrexate, or the maximum licensed dose of methotrexate is unable to achieve the treatment target of remission, alternate steroid-sparing disease modifying drugs may be prescribed as per the rheumatologist's usual clinical practice. This may either be as sequential monotherapy or add on combination therapy depending on preferences of the participant and the rheumatologist. All DMARDs licenced for management of RA are permitted for use in this trial.

- Participants may progress to biologic therapies and/or JAK inhibitors as per the NICE guidelines.
- Participants may use physiotherapy, occupational therapy or any other therapy input at the discretion of their rheumatologist.

Details of concomitant medications and treatments will be extracted from the participant's medical records including any changes to these treatments and dosage.

Methotrexate management during the trial

Participants randomised to subcutaneous methotrexate may switch to oral methotrexate or to another DMARD if there are any side-effects such as injection site reaction, or inability to self-inject, or lack of efficacy if the treating clinician feels that this is necessary, reflecting clinical practice.

Participants randomised to oral methotrexate will be able to switch to subcutaneous

methotrexate or to any other DMARD, for side-effects such as gastro-intestinal intolerance or lack of efficacy if the treating clinician feels that this is necessary, reflecting clinical practice.

7.9 Adherence

Participants adherence to their randomised treatment (oral or subcutaneous), as planned, will be recorded in the eCRF. Questions about specific treatment side effects (see section 4.3) will be collected by questionnaire and recorded on the eCRF.

At weeks 12, 24, and 52, methotrexate use and route will be recorded.

Participants adherence to their randomised treatment (oral or subcutaneous), as planned, will be monitored and reported regularly to the TMG according to the current version of the MOOSE monitoring plan.

7.10 Accountability for drugs & placebos

As the trial IMPs have marketing authorisation, clinic/pharmacy stocks will be used. Therefore, site and local pharmacies will follow their own local procedures for recording medication dispensed to trial participants. There is no requirement for participants to return unused IMPs back to the dispensing hospital or pharmacy.

Details of the trial medication taken e.g., weekly dose, and route of administration, will be recorded on the participant's eCRF and updated as needed if adjustments are made.

7.11 Management of trial drug overdose

Trial participants will be advised of the appropriate dose by their research clinician. Advice will also be given to follow the guidance on the enclosed leaflet. Trial drug overdose will be treated as per usual care.
Symptoms relating to trial drug overdose will be recorded as part of ongoing safety monitoring and reporting.

7.12 Urgent Safety Measures

Both trial IMPs have marketing authorisation and well characterised safety profiles thus urgent safety measures are not likely to be needed.

However, if an urgent safety measure is adopted, the MHRA will be notified in writing immediately and in any event no later than 3 days from the date the measures are taken. The sponsor and the relevant Research Ethics Committee (REC) will also be notified of the measures taken within the same time period. If needed, the sponsor will contact the MHRA Clinical Trials Unit and discuss the event with a safety scientist.

The DMC, in accordance with their charter, will be reviewing safety data at regular intervals throughout the trial and report any safety concerns as appropriate.

7.13 Protocol Deviations and Violations

Protocol non-compliance will be monitored via central monitoring of eCRF data. Where non compliances are detected they will be reviewed by the TMG and recorded, and escalated to sponsor and other committees as required.

Where the outcome of the initial assessment is a serious breach or other serious protocol violation, it will be reported immediately to the CI and further investigated following the relevant NCTU SOPs.

The CI will notify the Sponsor if a deviation or violation has an impact on participant safety or integrity of the trial data. The Sponsor will advise on appropriate measures to address the occurrence which may include reporting of a serious Good Clinical Practice (GCP) breach, conduct of an internal audit of the trial, and seeking counsel of the trial committees and the REC/MHRA.

7.14 Criteria for terminating trial

On the recommendation of the TSC, the sponsor (in collaboration with the TMG) may stop the trial if emerging evidence of efficacy or major safety concerns arise, or if there are significant concerns regarding trial conduct. There should be proof beyond reasonable doubt for overall efficacy or major safety concerns (internal or external evidence) for the TSC, DMC and TMG to recommend the trial is stopped.

Sites may be closed to recruitment prior to the end of the trial if the TMG identifies unacceptable performance related to monitoring triggers (outlined in the current version of the MOOSE Monitoring Plan).In the case where a site closure has been decided, the TMG may make this decision without consultation with the TSC.

8 STATISTICS and DATA MANAGEMENT PLAN

8.1 DATA MANAGEMENT PLAN (DMP)

Full details about data management will be provided in the Data Management Plan.

General

The DMP will include the agreed validation specification, roles and responsibilities for the trial data and user access. Additional manual and electronic reviews may also be conducted, and data queries / clarifications may arise from such reviews.

The trial database to be used is REDCap. It is a validated secure web-based platform which allows for data tracking via date stamped audit logs. MOOSE participants will be identified on REDCap only by a unique participant identifier (their trial/participant ID) to protect from bias and ensure confidentiality. Identifiable information will be stored within a restricted channel of the database for the purpose of questionnaire and treatment acceptability interview communication.

Data will be held on secure servers. These servers are located within The University of Nottingham data centres, which are managed and monitored regularly. Security is both physical (secure limited role-based access) and electronic (behind firewalls, access via user accounts (username and password) on encrypted connections, restricted access e.g. site

staff only have access to their site participant data, and by user type/role). All access and data transactions will be logged in a full audit trail.

An electronic copy of the video or audio-recordings of the qualitative interviews will be made by a professional transcription company who operate under strict terms of confidentiality. The transcript will then be pseudonymised. If direct quotations from the video/audio recording are included in future reports and publications, these will also be pseudonymised. Both the video/audio recording and the paper transcripts of interviews will be stored securely, and the pseudonymous transcript may be re-used by researchers in the future.

Data Capture and Data Queries

Only staff listed on the delegation log will be given access to the relevant sections of the trial database e.g. site 1 staff will only have access to site 1 trial participants while members of the NCTU trial team will have access to the wider database. Individual trial and research team member access will vary depending on role and associated blinding status.

Data will be collected from the patient medical notes and directly from the participant, either via online or paper questionnaire. Online questionnaires will be entered directly onto the secure trial database. Paper questionnaires will be returned to the NCTU and transcribed into the database by a member of the NCTU data team. Questionnaire data may be entered by the participant directly into the database, or collected from the participant and entered into the database on their behalf by site staff. Where paper questionnaires or CRF workbooks have been used to aid data collection, these will be classed as source data and transcribed into the secure trial database. All paper questionnaires and CRF workbooks completed at site is source data and will be collected and stored in the ISF.

The Qualitative researchers and designated members of the NCTU trial team will have access to an area of the database used only to contact and track contact of participants who have consented to be contacted about the treatment acceptability interviews.

Relevant regulatory authorities will also be permitted access onto the database.

Data reported on each eCRF will be checked for missing data or discrepancies and, where appropriate, will be queried. Staff delegated to complete eCRFs will be trained to adhere to relevant aspects of GCP associated with data entry.

Data queries will not be raised on questionnaires completed by the participants (online or paper). Questionnaires returned to NCTU will be transcribed by a member of NCTU and a minimum of 10% of questionnaires entered will be reviewed by a separate member of the data team. Where questionnaires have been transcribed by a member of staff, queries may be raised to check against source documentation. More information on questionnaire transcription is included in the MOOSE Data Monitoring Plan (DMP).

Description of Data Entry Validation

Programmed validation and manual checks will be used to identify data anomalies. All programmed validation checks are documented in the data dictionary and data quality rules on the REDCap database.

Programmed validation checks will automatically flag discrepancies at the point of data entry or will be executed by data management at the point of data cleaning. Data identified as missing or having discrepancies, may require a manual data query to be raised within REDCap by the Data Management team at NCTU.

Data Cleaning and Database Lock

Once all data has been collected and is cleaned and signed off by the PI, and all queries from the blind review meeting addressed, the trial database will be locked.

The database will be hard locked as per the relevant NCTU SOP using the associated checklist. All user rights will be removed, and it will be read only. Further details are included in the current version of the trial Data Management Plan.

Monitoring

On site and central monitoring will be carried out as required, following a risk assessment, and as documented in the current version of the trial monitoring plan. Any monitoring activities will be reported to the Sponsor and any issues noted will be followed up to resolution.

8.2 STATISTICS

8.2.1 Methods

The analysis and presentation of the trial results will be in accordance with the CONSORT guidelines and a full Statistical Analysis Plan (SAP) will be developed prior to database lock. The trial statistician will be responsible for these. The primary objective of the trial is to determine the effectiveness of first line subcutaneous versus oral methotrexate and as such, the principal approach to our primary comparative analysis will be to analyse as randomised without imputation of missing data, with due emphasis being placed on the confidence intervals for the between arm comparisons. Sensitivity and secondary analyses will be considered supportive to the primary.

Characteristics and baseline data of randomised participants in the two trial arms at baseline will be described, using appropriate descriptive statistics. The primary, secondary and safety outcomes will be assessed as described in the following sections.

Sample size and justification

The sample size is based on the primary outcome – the proportion of participants showing remission defined as a DAS-28-CRP <2.6, 24 weeks from randomisation. A survey of 33 rheumatologists in June 2020 indicated that 13 (39%) and 29 (89%) would prescribe subcutaneous methotrexate if it increased remission by 15% or 20% respectively. Given this marked difference, the trial was powered to detect an absolute difference of 17.5% between oral and subcutaneous methotrexate. Assuming that 30% of participants in the oral methotrexate arm were in remission at week 24 [14], 173 participants would be required in each arm to detect a difference of 17.5% (i.e. 47.5% of participants in the subcutaneous arm in remission), with (90% power, and a 2-sided alpha of=5%). Assuming 10% loss to follow-up at 24 weeks, 386 participants should be randomised. Since the primary objective of the trial is to assess the relative effectiveness of first line subcutaneous versus oral methotrexate, the primary comparison will be as randomised (i.e. intention to treat). Therefore, no additional adjustments to the sample size are necessary. Power calculations were performed using PASS v12 (NCSS).

Assessment of efficacy

Primary outcome: The evaluation of the primary outcome will be performed using a mixed effects model for binary outcomes that includes study centre and disease duration as per the minimisation, and baseline DAS-28-CRP calculated using the CRP value obtained on the day of randomisation (the DAS-28-CRP used in the minimisation used a CRP value taken previously due to results not being available on the same day's sampling).

The primary estimands comparing the proportion of participants in remission at 24 weeks between those randomised to first line subcutaneous methotrexate and first line oral methotrexate, regardless of whether participants do not take or discontinue assigned treatment, or start a new treatment as add on or replacement therapy, will be the adjusted risk difference and 95% confidence interval. Sensitivity analyses using techniques such as multiple imputation will investigate the impact of missing data.

Non-compliance (intercurrent events): It is known that some participants may have their first line therapy discontinued due to lack of efficacy or tolerability or have additional therapies added to that first line therapy. 55 of the 151 participants randomised to the intensive treatment arm in the CAMERA study swapped from oral to subcutaneous methotrexate injections for either intolerance or lack of efficacy and 20% participants prescribed oral methotrexate in the CATCH cohort swapped from oral to subcutaneous and 3% vice versa [8, 15]. In addition, participants may not take their medications as directed and may receive rescue medications on a planned temporary basis (e.g., corticosteroids to treat RA flares). We will therefore collect data to allow us to characterise and investigate such intercurrent events
and estimate the efficacy of the two treatments despite the pragmatic trial design.

Secondary outcomes: Secondary outcomes will be analysed using appropriate regression models that include site and disease duration as recorded for minimisation, and DAS-28-CRP calculated using all components as collected at baseline, and baseline values of that outcome if measured and will be as randomised without imputation of missing data, unless otherwise indicated in the SAP.

Many of the secondary outcomes are closely correlated but are produced to allow between trial comparisons. Specific estimates should be treated with due caution, and interpretation should take into account consistency between these outcomes.

Treatment acceptability outcomes will be assessed using the same approach as outlined in earlier sentence. Additionally, using the Beliefs about Medicines Questionnaire a Necessity-Concerns Differential will be calculated. This score will provide a numerical indicator of how participants judge their personal need for different formulations of methotrexate relative to their concerns about the potential negative effects of taking methotrexate.

Sub-group analyses: The comparison of first line subcutaneous and oral methotrexate on the primary outcome only will be performed in subgroups according to disease duration (less-than 4 months, 4 – 12 months, and more than 12 months), auto-antibody status (only RF positive, only anti-CCP positive, dual sero-positive, seronegative), body mass index (≥30 vs. <30 kg/m2) and smoking status (current-smoker vs. not-currently smoking at the screening visit). The interpretation of any subgroup effect will be based on interaction tests (i.e. evidence of differential treatment effects in the different subgroups). It is acknowledged that these investigations will not be adequately powered.

Assessment of safety

Safety data: Safety data such as infections, side effects and adverse events will be reported by the interval in which they were collected (for example baseline to week 4, week 4 to week 8 etc), and over the whole trial. The incidence and severity will be summarised using descriptive statistics, according to the treatment the participant was randomised to. The treatment the participant was receiving at the time of the event will be recorded and further summaries may be produced using this information. Further details will be specified in the SAP.

Procedures for missing, unused and spurious data

Spurious data will be queried using processes documented in the data management plan. Where appropriate, self-evident corrections may be made. All attempts will be made to collect missing data. Where data remains missing, investigations will be made to assess whether these data are likely to be missing completely at random. The primary analyses will not use any imputation techniques. However, the SAP will document where methods to address missing data (for example multiple imputation in a sensitivity analysis) will be used.

Definition of populations analysed

Intention to treat dataset: All randomised participants are summarised/analysed according to their randomised treatment irrespective of the treatment(s) they actually received. This is the primary dataset to be used in both the effectiveness and the safety analyses.

Safety dataset: All randomised participants are summarised according to the treatment they actually receive, irrespective of their randomised allocation. This dataset may be used for sensitivity analyses.

9 QUALITATIVE TREATMENT ACCEPTABILITY STUDY

As highlighted in Table 4 the Theoretical Framework of Acceptability questionnaire will be part of the survey participants complete at week 4, 24 and 52. This section now outlines the qualitative study which will be embedded during the trial. The overall aim of the qualitative study is to explore perceptions of acceptability of taking methotrexate either orally or by injection in adults newly diagnosed with Rheumatoid Arthritis.

Objectives

1. Explore trial participants' beliefs about and experiences with methotrexate either orally or by injection
2. Describe the development of perceptions of acceptability in the first 6 months of treatment
3. Explore how perceptions of acceptability and beliefs about methotrexate affect adherence to methotrexate either orally or by injection

Qualitative data collection will involve semi-structured interviews in both arms. Maximum variance sampling will ensure participant diversity e.g. age, gender, ethnicity, health literacy, perceptions of acceptability. We aim to interview approximately 10 participants in each arm depending on data saturation. All those interviewed at 4-8 weeks will be invited to another interview between 24-32 weeks. This longitudinal qualitative design provides enhanced

understanding of treatment acceptability and adherence over time and helps to explain any variations in outcomes. Health literacy is not an outcome, but data will be collected using a single item screening question at baseline to sample participants for interview studies (36).

Interviews will be transcribed verbatim and analysed thematically using a framework approach [16, 17]. Following data familiarisation, a thematic framework will be developed using inductive and deductive coding [17]. For longitudinal analysis, summaries of each participant's data [18, 19] will be used to identify perceptions of changes in acceptability of interventions and influences of change within case (each person) and in each intervention group (cross-case). Interpretation of data will be discussed with PPI members and with researchers from different professional backgrounds (e.g. rheumatology, health services research), improving the trustworthiness of analysis [17, 20]. The qualitative analysis will be merged with the quantitative analysis (from the TFA questionnaire) to provide enhanced understanding of treatment acceptability and adherence and to help explain any variations in trial outcomes.

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10 HEALTH ECONOMICS

10.1 Aim

The aim of the health economics will be to determine the cost-effectiveness of subcutaneous methotrexate compared to oral methotrexate. The analyses will be in line with the NICE reference case, estimating a cost per quality-adjusted life year (QALY) gained for the more efficacious treatment from a probabilistic analysis [21]. Currently NICE state that "*Below a most plausible* incremental cost-effectiveness ratio *(ICER) of £20,000 per QALY gained, the decision to recommend the use of a technology is normally based on the cost-effectiveness estimate*".

10.2 Methods

Two sets of modelling will be undertaken. The first model will be restricted to the duration of the trial so that only the observed outcomes contribute directly to the estimate of the ICER. The second model explicitly acknowledges that there may be benefits (and cost offsets, in particular those associated with increased biologic disease modifying antirheumatic drugs and potentially joint surgery) accrued beyond the duration of the trial associated with subcutaneous methotrexate use and would use mathematical modelling techniques to extrapolate into the future to provide an ICER estimated over a longer period of time.

10.3 Health care resource use: health service, social and societal costs

The model will use an NHS and personal social services cost perspective as recommended by NICE. Cost-estimates will be taken from standard literature sources, such as the British National Formulary or NHS Reference Costs. The costs of adverse events will be chosen following targeted literature reviews, as will any QALY impact if it is likely that these patients' harms would not be captured in the EQ-5D questionnaires which have an immediate recall period[24].

10.4 Outcome Measures

The use of the QALY as a metric allows the cost-effectiveness of strategies to be compared with other interventions competing for NHS resources. If the team deems it appropriate other outcome measures in the modelling will be reported.

10.5 Analysis

For both models the mean ICER estimated from probabilistic analyses will be calculated. The uncertainty in these ICERs will be explored, using seemingly unrelated regression for the first model [22] and for the second by estimating the confidence interval in the calculated ICERs presented, alongside an estimate in the true underlying uncertainty using a percentile approach [23]. In order to visualise the uncertainty, cost-effectiveness planes and cost-effectiveness acceptability curves will be provided.

Comprehensive scenario / sensitivity analyses will be undertaken to explore the robustness of the results to changes in the values of key parameters (such as the projected use of biologic disease modifying anti-rheumatic drugs (e.g. anti-TNF agents), requirement for surgery and utility values for patients) to alternative plausible values, and by the inclusion of monetised values for absenteeism and presenteeism.

If appropriate, value of information analyses will be conducted to show whether there is an incentive to collect further information, and on which parameters[24, 25]. The results from the value of information analyses will indicate the maximum cost of research to reduce decision uncertainty and will indicate whether further research would be seen as cost-effective.

11 ADVERSE EVENTS

11.1 Definitions

An **adverse event (AE**) is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the trial.

An AE does include a / an:
1. Exacerbation of a pre-existing illness.

2. Increase in frequency or intensity of a pre-existing episodic event or condition.

3. Condition detected or diagnosed after medicinal product administration even though it may have been present prior to the start of the trial.

4. Continuous persistent disease or symptoms present at baseline that worsen following the start of the trial.

An AE does not include a / an:
1. Medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that lead to the procedure is an AE.

2. Pre-existing disease or conditions present or detected at the start of the trial that did not worsen.

3. Situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and / or convenience admissions).

4. Disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition.

5. Overdose of concurrent medication without any signs or symptoms.

Methotrexate is a treatment that is available within the NHS and is used in standard care for the treatment of RA. As the safety profiles of the IMPs used in this trial are well characterised, we will adopt a targeted approach to AE reporting. We will exclude all adverse events due to disease progression from expedited reporting. Specific known treatment related AEs will be collected as part of the participant questionnaires, as outlined in Appendix 1 , 'Severity of Methotrexate Side Effect'.. Additional AEs reported by participants will be collected and reported on the adverse event log.

Events collected as part of the CRF (not on the adverse event log) do not require reporting as part of the APR or DSUR.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) as per NCTU standard practice.

Common toxicity criteria for adverse events: Known AEs to be collected to assess tolerability of randomised treatment are, abdominal pain, nausea, vomiting, diarrhoea, bloating, oral mucositis and injection site reaction.

Infection information will be collected as part of each follow-up questionnaire relating to recent diagnoses of herpes zoster (shingles), urinary tract infections requiring antibiotics, chest infections/pneumonia requiring antibiotics, cellulitis requiring antibiotics and COVID-19.

Blood test results will be reviewed as part of usual care to identify abnormal results. Abnormal results relating to leucocyte count, neutrophil count, platelet count, ALT level, AST level, and creatine level will be recorded in the CRF. Where abnormal results meet the seriousness criteria, these should be reported to the NCTU in accordance with the procedure outlined in 11.4.

As methotrexate is a long-established drug, no safety signal are expected in these blood tests. Both oral and subcutaneous routes are well established modes of administering methotrexate in the treatment of RA. Abnormalities will be managed by the local usual care team and any SAE and/or SUSAR data will be reported to the DMC at their annual meeting.

A **Serious Adverse Event (SAE)** is any adverse event occurring following trial mandated procedures, having received the IMP or placebo that results in any of the following outcomes:

1. Death

2. A life-threatening adverse event

3. Inpatient hospitalisation or prolongation of existing hospitalisation

4. A disability / incapacity

5. A congenital anomaly in the offspring of a participant

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All adverse events will be assessed for seriousness, expectedness and causality.

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

11.2 Causality

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial treatment administration which makes a causal relationship incompatible or for which other drugs, chemicals or disease provide a plausible explanation**.** This will be counted as “unrelated” for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, but which could also be explained by other drugs, chemicals or concurrent disease. This will be counted as “related” for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and is unlikely to be due to other drugs, chemicals or concurrent disease. This will be counted as “related” for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as “related” for notification purposes.

An AE whose causal relationship to the trial IMP is assessed by the Chief Investigator as “possible”, “probable”, or “definite” is an Adverse Reaction (AR) or Serious Adverse Reaction (SAR.

With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

11.3 Expectedness

Expectedness of reported SAEs will be determined by the local PI or nominated delegate.

Expectedness of SARs will be determined by the CI or nominated deputy (identified at the outset of the trial) according to the relevant IMP trial SmPC. An AE that is listed in the approved SmPC will be characterised as ‘expected’ whilst not listed AEs will be characterised as ‘unexpected’.

11.4 Reporting of adverse events

Reporting Timelines
Participants will be asked to report any AEs they are experiencing/have experienced at each clinical visit (see section 7 Trial Treatment and Regimen).

In the event of an SAE, participants will be asked to contact the study site immediately and the site team should submit an SAE form to the NCTU immediately/within a day of being notified of the event.

SAEs will be collected from the day of randomisation until the end of the follow-up period (52 week clinical visit). All adverse events will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the trial medication or treatment is not the cause.

On becoming aware that a participant has experienced an SAE, the Investigator (or delegate) must complete, date and sign an SAE Form. The form should be emailed to the NCTU as soon as possible and no later than 24 hours after first becoming aware of the event:

NCTU-sae@nottingham.ac.uk

The CI (delegated responsibility by the Sponsor) shall be informed immediately (within 24 hours) of any serious adverse events reported to the NCTU and shall determine seriousness, expectedness and causality in conjunction with any treating medical practitioners.

Routine hospitalisations for pre-existing medical conditions do not require reporting as an SAE.

11.5 Notification of pregnancy

Where a site becomes aware of a pregnant participant during the trial a Notification of Pregnancy form will be completed and returned to NCTU, and the participants GP notified of the pregnancy. Pregnant participants must stop methotrexate and be followed up as part of their routine care. Incidents of pregnancies are not required to be followed-up as part of trial reporting.

11.6 Urgent Safety Measures

Both trial IMPs have marketing authorisation and well characterised safety profiles thus urgent safety measures are not likely to be needed.

However, if an urgent safety measure is adopted, the MHRA will be notified in writing immediately and in any event no later than 3 days from the date the measures are taken. The sponsor and the relevant Research Ethics Committee (REC) will also be notified of the measures taken within the same time period. If needed, the sponsor will contact the MHRA Clinical Trials Unit and discuss the event with a safety scientist.

The DMC, in accordance with their charter, will be reviewing safety data at regular intervals throughout the trial and report any safety concerns as appropriate.

11.7 SUSARs

A serious adverse event that is either sudden in its onset (anaphylaxis), unexpected in its severity and seriousness or not a known side effect of the IMP *and* related or suspected to be related to the IMP is classed as Suspected Unexpected Serious Adverse Reaction and requires expedited reporting as per the clinical trials regulations.

All serious adverse events that fall or are suspected to fall within these criteria shall be treated as a SUSAR until deemed otherwise.

The event shall be reported immediately (within 24 hours) of knowledge of its occurrence to the NCTU who will report to the CI.

It is the responsibility of the CI (with tasks delegated to NCTU as appropriate) to:

- Assess the event for seriousness, expectedness and relatedness to the trial IMP
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action.
- If the event is deemed a SUSAR, within seven days, enter the required data on the MHRA's ICSR Submissions website.
- Inform the REC using the reporting form found on the HRA web page within 7 days of knowledge of the event.
- Within a further eight days send any follow-up information and reports to the MHRA and REC.
- Make any amendments as required to the trial protocol and inform the ethics and regulatory authorities as required.

Participant removal from the trial due to adverse events
Any participant who experiences an adverse event may be withdrawn from the trial at the discretion of the Investigator.

12 ETHICAL AND REGULATORY ASPECTS

12.1 ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC), the respective National Health Service (NHS) or other healthcare provider's Research & Development (R&D) department, and the Health Research Authority (HRA) if required. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant and GP information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the MHRA, R&D and REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, in accordance with the

Medicines for Human Use Regulations, Statutory Instrument 2004, 1031 and its subsequent amendments and the UK Department of Health Policy Framework for Health and Social Care, 2017.

12.2 INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant shall both sign and date the Consent Form before the person can participate in the trial.

The participant will receive a copy of the signed and dated forms and the original will be retained in the ISF. A copy will be uploaded to REDCap, and a second copy will be filed in the participant's medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial.

The decision regarding participation in the trial is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding trial participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be performed before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the trial, and will discuss with them, whether they wish to continue with the trial. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the trial, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

12.3 RECORDS

Drug accountability

There are no trial-specific accountability requirements; sites and/or local pharmacies will follow their own local procedures for recording treatments dispensed.

Drug supplies will be kept in a secure, limited access storage area under the storage conditions specified by each pharmacy. Accountability logs will not be required as trial IMPs will be obtained via standard prescriptions dispensed by local pharmacies/clinic stocks. Methotrexate dose and dose escalations will be recorded in the patient's medical records and within each participant's assessment visit eCRF.

Case Report Forms

Each participant will be assigned a trial identity code number, allocated at randomisation for use on eCRFs, other trial documents and the electronic database. The documents and database may also use date of birth (dd/mmm/yyyy).

eCRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, and Participant Trial Number (the Trial Recruitment Log), to permit identification

of all participants enrolled in the trial in accordance with regulatory requirements and for follow-up as required.

eCRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the eCRF.

Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, paper questionnaire booklets, paper CRF workbooks where used, laboratory results and pharmacy records. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements (section 13.6). Where postal questionnaires are returned to the NCTU they will be filed as source data as part of the TMF.

Direct access to source data / documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities (MHRA).

12.4 DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 2018. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).
Information about the trial in the participant's medical records will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

13 QUALITY ASSURANCE & AUDIT

13.1 INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff with both public liability insurance and clinical trials insurance in respect of claims made by research subjects.

The University of Nottingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

13.2 TRIAL/STUDY CONDUCT

Trial conduct will be subject to systems audit of the TMF for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; drug accountability, pharmacy records and equipment calibration logs.

The NCTU QA team shall carry out systems and trial audits as part of the NCTU risk adapted annual audit programme. Should this trial be selected for audit, an audit report shall be issued to the Trial Manager and can be disseminated to the appropriate committees should this be appropriate. Where monitoring has identified the need for a site audit, or this is requested of the TMG/TSC, this shall be carried out by a trained member of NCTU staff.

13.3 TRIAL DATA

Monitoring will be carried out as required following a risk assessment and as documented in the monitoring plan. NCTU will be in regular contact with the site research team to check on progress and address any queries that they may have. The trial team will check incoming Case Report Forms for compliance with the protocol, data consistency, missing data and timing. Sites will be asked for missing data or clarification of inconsistencies or discrepancies Additional on-site monitoring visits may be triggered, for example by poor CRF return, poor data quality, lower than expected SAE reporting rates, excessive number of participant withdrawals or deviations. If a monitoring visit is required, NCTU will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow NCTU trial staff access to source documents as requested.
Trial data and evidence of monitoring and systems audits will be made available for inspection by the regulatory authority as required.

13.4 RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the trial. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the trial records, a second person will be nominated to take over this responsibility. Recordings and transcripts from the qualitative interviews will be retained for a minimum of 10 years in line with Keele's local policy.

The TMF and trial documents held by the NCTU on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

13.5 DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee and the funder (NIHR HTA) as appropriate in making this decision.

13.6 STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this trial are considered confidential and disclosure to third parties is prohibited with the exceptions noted above. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare. If information is disclosed during the trial that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

14 PUBLICATION AND DISSEMINATION POLICY

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the TMG, led by the Chief Investigator who will be the first and corresponding author. All co-authors will meet authorship criteria. The remaining authorship will be determined by mutual agreement. Results may also be published on relevant websites and presented at conferences.

Participants will receive regularly newsletters to update on trial news and progress. Participants will be notified of the results in an end of trial letter and will be able to view the results on the website.

Any publications and presentations prepared by Investigators must be reviewed by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Participants will not be identified in any publications or presentations. Publications and presentations (other than the protocol) will typically happen after the end of the trial.

De-identified individual participant data may be shared with researchers external to the trial research team in accordance with the NCTU's Data Sharing Standard Operating Procedure (SOP 33) wherein the request is considered by a data sharing committee which includes the CI and the sponsor and where a formal data sharing agreement is required between the trial sponsor (University of Nottingham) and the sponsor of the data requestor.
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15 USER AND PUBLIC INVOLVEMENT

The perspectives of RA patients are key to this research. Patient and Public Involvement (PPI) will be embedded throughout the project to ensure impact and value to the research.

A PPI group consisting of RA patients and/or carers will be involved in the research at key stages. This group will contribute to the trial design and implementation including development of participant information, recruitment strategies, data collection and retention.

Our PPI co-applicant will attend TMGs. Where appropriate, and in line with UK standards for PPIE, information from TMGs will be shared with the PPI group. . This may include updates on recruitment, strategies, and retention. They will also be contacted on an ad-hoc basis outside these scheduled meetings as-and-when issues with recruitment arise. We will also invite a lay member of the public to join the TSC (who will also be independent of our PPI panel).

There will also be a range of flexible opportunities for participating in project feedback and dissemination activities including publication authorship and presenting at conferences to highlight the trial findings.

At the end of the trial, a PPI meeting will be arranged to disseminate the trial findings.

PPIE group members will be reimbursed accordingly, with appropriate remuneration and recognition being established for each group as per guidance from NIHR Involve. A budget has been allocated for PPI training and learning events to ensure our PPI group are supported in gaining the necessary skills, which may include learning about research design and good clinical practice.

16 TRIAL FINANCES

16.1 Funding source

This trial is funded by the NIHR, Health Technology Assessment programme; Project Reference Number: NIHR132711. The funder is not involved in the conduct, analyses interpretation or reporting of the trial.

16.2 Participant stipends and payments

Participants will not be paid to participate in the trial. At the baseline appointment, and at the 24 week visit, participants will receive a £25 shopping voucher. This is a thank you for the time taken to fill in the initial questionnaires and to travel to appointments that are not part of the usual NHS care.

17 Appendix 1

Derivation of outcomes

	Description	Used in
Disease activity and treatment response		
DAS-28-CRP	**Score** DAS-28-CRP = 0.56*√(TJC) +0.28*√(SJC) +0.014*GH+0.36*ln(CRP+1)+0.96 The CRP used in the calculation should be the one taken on the day the tender and swollen joint counts and the GH (assessed by question - How active was your arthritis during the past week, recorded in the patient questionnaire – about your arthritis) assessments were made. **Definition of remission** DAS-28-CRP <2.6 **Treatment response** Response to treatment measured using EULAR criteria is described as: • For patients with baseline DAS-28-CRP ≤3.2: - DAS-28-CRP improvement >1.2: good response - DAS-28-CRP improvement ≤1.2 and >0.6: moderate response to treatment - DAS-28-CRP improvement ≤0.6: no response • For patients with baseline DAS-28-CRP >3.2 and ≤5.1: - DAS-28-CRP improvement >0.6 defined as moderate response to treatment - DAS-28-CRP improvement ≤0.6 defined as no response to treatment	PE1, E1, E8, E9

	Description	Used in
	• For patients with baseline DAS-28-CRP >5.1: - DAS-28-CRP improvement >1.2 defined as moderate response to treatment - DAS-28-CRP improvement ≤1.2 defined as no response to treatment	

	Description	Used in
SDAI	**Score** SDAI = TJC + SJC + PGA + PhGA + CRP **Disease activity** SDAI scores are interpreted as: - 0.0 – 3.3: Remission - 3.4 – 11: Low activity - 11.1 – 26.0: Moderate activity - 26.1 – 86: High activity	E2, E6, E10
CDAI	**Score** CDAI = TJC + SJC + PGA + PhGA **Disease activity** CDAI scores are interpreted as: - 0-2.8 – Remission - 2.9-10 – Low activity - 10.1 – 22 – Moderate activity - 22.1 – 76 – High activity	E3, E5, E11
ACR/EULAR 2022 Boolean	**Definition of remission:** - TJC ≤ 1 - SJC ≤ 1 - PGA (0 – 10) ≤ 1 - CPR (mg/dL) ≤ 1	E4

	Description	Used in
ACR20/50/70	ACR20/50/70 is described as 20% / 50% / 70% improvement in tender and swollen joint counts and 20% / 50%/ 70% improvement in at least three of the five parameters: - Patient global health (PGH) - Physician global assessment (PhGA) - Patient pain - HAQ-DI - CRP	E7
Assessment components		
Swollen joint count (SJC)	28 joint count	PE1, E1 – E12
Tender joint count (TJC)	28 joint count	PE1, E1 – E11, E13
Patient global assessment (PGA)	Scale 0 – 10 with 0.5 increment. PGA will be assessed using the question - Considering all the ways your arthritis affects you, rate how well you are doing.	E2, E3, E4, E5, E6, E10, E11, E14
Physician global assessment (PhGA)	Scale 0 – 10 with 0.5 increment. PhGA will be assessed by item - Provider Global Assessment of Disease Activity.	E2, E3, E5, E6, E7, E10, E11, E15
Patient global health (ACR question) (PGH)	Scale 0 – 100 (VAS) PGH will be assessed using the question - Considering all the ways in which illness and health conditions may affect you at this time, please make a mark to show how you are doing.	E7, E16

	Description	Used in
CRP	Unit of CRP is mg/L for DAS-28-CRP and mg/dL for SDAI.	PE1, E1 – E11, E17
Patient pain	Scale 0 – 100 (VAS) Patient pain will be assessed using the question - How much pain have you had because of your condition over the past week.	E7, E18
Patient health		
HAQ-DI	Health Assessment Questionnaire Disability Index (range: 1 – 3) is formed by 20 items in 8 categories. Each subcategory question can be scored from 0 to 3. Score of each category will be determined by the highest subcategory score. If aids/devices/help from another person are checked for a category, the score of the category will be set to '2', unless it is already '3'. Sores of eight categories will be averaged into an overall HAQ-DI score. Function is categorised as: - HAQ-DI <1: mild difficulty - HAQ-DI ≥1 and <2: moderate difficulty - HAQ-DI ≥2 and <3: severe difficulty - HAQ-DI=3: very severe difficulty	E7, E19
FACIT-F	FACIT-F (range: 0 – 160) consists of 40 items in 5 subscales. Each item is scored from 0 to 4. Score of each subscale is calculated by multiplying the total subscale score by the number of items answered. More than 50% of the items in a subscale need to be answered to compute a valid score. Total score of FACIT-F is the sum of the scores of 5 subscales. Higher score indicates better of quality of life.	E20

	Description	Used in
GAD-7	GAD-7 (range: 0 – 21) consists of 7 items. Each item can be scored from 0 to 3. Total score is the sum of the scores of 7 items. Anxiety is categorised as: - GAD-7 score 0 – 4: minimal anxiety - GAD-7 score 5 – 9: mild anxiety - GAD-7 score 10 – 11: moderate anxiety - GAD-7 score >15: severe anxiety	E21
PHQ-8	Patient Health Questionnaire depression scale (PHQ-8) consists of 8 questions with each question scores from 0 – 3. Total score of PHQ-8 is the sum of the scores of the 8 questions. Total score will be set to be missing if more than 1 item missing. Depression can be categorised as: - PHQ-8 score <10 defined as normal - PHQ-8 score ≥10 defined as current depression	E22
Treatment acceptability		
TFA	Theoretical Framework of Acceptability Questionnaire (TFAQ) consists of 8 components: - Affective attitude: 1 = strongly dislike to 5 = strongly like - Burden: 1 = no effort at all to 5 = huge effort - Ethicality / Perceived effectiveness / Intervention coherence / Opportunity costs: 1 = strongly disagreed to 5 = strongly agreed - Self-efficacy: 1 = very unconfident to 5 = very confident - General acceptability: 1 = completely unacceptable to 5 = completely acceptable	E23
BMQ	Beliefs about Medicines Questionnaire (BMQ) consists of two 5-items scales. Each item scores from 1 = strongly disagreed to 5 = strong agreed. Total score of each scale is the sum of 5 items (range: 5 – 25). Higher score indicates stronger beliefs.	E24
Quality of life		

	Description	Used in
EQ-5D-5L	EQ-5D-5L comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state.	E25
RA-QoL	RA-QoL consists of 30 items with responses yes/no. Score of RA-QoL is the sum of questions with response 'yes' (range: 0 – 30). Higher score indicates poor quality of life.	E26
WPAI	WPAI questionnaire that consists of 6 questions. Four main outcomes in relation to the work productivity due to RA are calculated as: - Percentage of the worked time missed due to RA = Q2/(Q2+Q4) * 100 - Percentage of impairment while working due to RA = Q5/10 * 100 - Percentage of overall work impairment due to RA = [Q2/(Q2+Q4) + (1-Q2/(Q2+Q4)) * (Q5/10)] * 100 - Percentage of activity impairment due to RA: Q6/10 * 100	E27
Treatment pathway		
Usage of corticosteroids	The proportion of participants having at least one course of corticosteroids (or corticosteroid injection) in the previous 4 weeks or on the day of assessment will be collected at 12, 24 and 52 weeks. Information on the route of corticosteroid injection – intra-muscular or intra-articular will be recorded. For those taking oral corticosteroids on the day of assessment, their current daily corticosteroid dose will be recorded.	E28

	Description	Used in
Discontinuation of randomised treatment	Proportion of participants who discontinue the randomised drug. Time from randomisation date to discontinuation date. Censor participants who are still having randomised treatment.	E29, E30
Start on any additional/alternative DMARDs	Proportion of participants who start on additional/alternative DMARDs. Time from randomisation date to the date of start on any additional/alternative DMARDs. Censor participants who have not started any additional/alternative drug up 52 weeks post randomisation.	E31, E32
Start on biologic drug	Proportion of participants who have started a biological drug (either as monotherapy or combination therapy). Time from randomisation date to the date of start on biologic drug. Participants will be censored at 52 weeks post randomisation if they have not started a biologic drug.	E33, E34
Safety		
Type of infection	- Herpes Zoster (Shingles) - Urinary tract infection requiring antibiotics - Chest infection or pneumonia requiring antibiotics - Skin or soft tissue infection (also called cellulitis) requiring antibiotics - COVID-19 (must have had a positive PCR or lateral flow test)	S1
Type of methotrexate side effect	- Nausea - Abdominal Pain - Bloating of the abdomen - Diarrhoea - Vomiting - Mucositis (oral)	S2

<table>
<tr><th></th><th>Description</th><th>Used in</th></tr>
<tr><td></td><td>- Injection site reaction (methotrexate injection only)</td><td></td></tr>
<tr><td>Severity of methotrexate side effect</td><td>Severity of methotrexate side effects is defined:

- Mild (Grade 1)
- Moderate (Grade 2)
- Severe (Grade 3)

Definition of severity is based on CTC criteria. Details of Grade1 – Grade 3 are listed below:

<table>
<tr><th>Symptom</th><th>Mild (Grade 1)</th><th>Moderate (Grade 2)</th><th>Severe (Grade 3)</th></tr>
<tr><td>Nausea</td><td>Loss of appetite without affecting usual eating habits</td><td>Loss of appetite with eating less than usual but no significant weight loss</td><td>Loss of appetite with eating less than usual and a significant amount of weight loss</td></tr>
<tr><td>Abdominal pain</td><td>No effect on activities</td><td>Pain interfered with daily living activities</td><td>Pain stopped patients from caring for themselves</td></tr>
<tr><td>Bloating</td><td>No effect on eating, drinking, or usual bowel movements</td><td>Affected usual eating or drinking habits, or change in bowel movements</td><td>-</td></tr>
<tr><td>Diarrhoea</td><td>1-3 more stools than usual per day</td><td>4-6 more stools than usual per day or interfered with daily living activities</td><td>7 or more stools than usual per day or stopped patients from taking care of themselves</td></tr>
</table></td><td>S2</td></tr>
</table>

<table>
<tr><th></th><th>Description</th><th>Used in</th></tr>
<tr><td></td><td>
<table>
<tr><td>Vomiting</td><td>No effect on activities</td><td>Medical help indicated</td><td>Hospital admission</td></tr>
<tr><td>Mucositis (oral)</td><td>Mild or no symptoms</td><td>Moderate pain that didn’t interfere with eating habits</td><td>Severe pain that led to eating less</td></tr>
<tr><td>Injection site reaction</td><td>Pain at the injection site when touched</td><td>Pain at the injection site even when it was not touched</td><td>Swelling, lumpy soft-tissue, ulcers or spreading red streaks at the injection site</td></tr>
</table>
Grade 4 and Grade 5 will be collected via SAE reports.
</td><td></td></tr>
<tr><td>Bloods tests for leucocyte count, neutrophil count, platelet count, ALT, AST, creatinine, and MCV.</td><td>Blood test results will be collected using medical record. Test results will be summarised and categorised according to the common toxicity criteria for adverse events.</td><td>S5</td></tr>
</table>

19 SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name) Abhishek Abhishek

Signature: Abhishek Abhishek (Jul 4, 2025 13:16 GMT+1)

Date: _____

Trial Manager: (name) Sarah McClure

Signature: _____

Date: 04 July 2025

Trial Statistician: (name) Yuanfei Su

Signature: _____

Date: 06/19/2025

20 REFERENCES

1. Abhishek, A., et al., *Rheumatoid arthritis is getting less frequent-results of a nationwide population-based cohort study.* Rheumatology (Oxford), 2017. **56**(5): p. 736-744.
2. van der Linden, M.P., et al., *Long-term impact of delay in assessment of patients with early arthritis.* Arthritis Rheum, 2010. **62**(12): p. 3537-46.
3. Edwards, C.J., et al., *Regional and temporal variation in the treatment of rheumatoid arthritis across the UK: a descriptive register-based cohort study.* BMJ Open, 2012. **2**(6).
4. Braun, J., et al., *Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial.* Arthritis Rheum, 2008. **58**(1): p. 73-81.
5. Islam, M.S., et al., *Comparative efficacy of subcutaneous versus oral methotrexate in active rheumatoid arthritis.* Mymensingh Med J, 2013. **22**(3): p. 483-8.
6. Dhaon, P., et al., *Oral Methotrexate in split dose weekly versus oral or parenteral Methotrexate once weekly in Rheumatoid Arthritis: a short-term study.* Int J Rheum Dis, 2018. **21**(5): p. 1010-1017.
7. Bujor, A.M., et al., *Comparison of oral versus parenteral methotrexate in the treatment of rheumatoid arthritis: A meta-analysis.* PLoS One, 2019. **14**(9): p. e0221823.
8. Hazlewood, G.S., et al., *The comparative effectiveness of oral versus subcutaneous methotrexate for the treatment of early rheumatoid arthritis.* Ann Rheum Dis, 2016. **75**(6): p. 1003-8.
9. Schiff, M.H., J.S. Jaffe, and B. Freundlich, *Head-to-head, randomised, crossover study of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis: drug-exposure limitations of oral methotrexate at doses >/=15 mg may be overcome with subcutaneous administration.* Ann Rheum Dis, 2014. **73**(8): p. 1549-51.
10. Ledingham, J., et al., *BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs.* Rheumatology (Oxford), 2017. **56**(12): p. 2257.
11. Cresswell, J., *A concise introduction to mixed methods research*. 2014: Sage Publishing.
12. Sekhon, M., M. Cartwright, and J.J. Francis, *Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework.* BMC Health Serv Res, 2017. **17**(1): p. 88.
13. Horne, R., *Compliance adherence and concordance*, in *Pharmacy Practice*. 2001, Taylor and Francis. p. 148.
14. Emery, P., et al., *Pragmatic randomised controlled trial of very early etanercept and MTX versus MTX with delayed etanercept in RA: the VEDERA trial.* Ann Rheum Dis, 2020. **79**(4): p. 464-471.
15. Verstappen, S.M., et al., *Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial).* Ann Rheum Dis, 2007. **66**(11): p. 1443-9.

16. Ritchie, J.S., L, *Analysing qualitative data*, in *Analysing qualitative data*, A.B. Bryman, R. G, Editor. 1994, Routledge. p. 246.
17. Gale, N.K., et al., *Using the framework method for the analysis of qualitative data in multi-disciplinary health research.* Bmc Medical Research Methodology, 2013. **13**.
18. Plano Clark, V.L., et al., *Practices for Embedding an Interpretive Qualitative Approach Within a Randomized Clinical Trial.* Journal of Mixed Methods Research, 2013. **7**(3): p. 219-242.
19. Saldaña, J., *Longitudinal qualitative research: Analyzing change through time*. 2003: Rowman Altamira.
20. Schielke, H.J., et al., *Creative consensus on interpretations of qualitative data: the Ward method.* Psychother Res, 2009. **19**(4-5): p. 558-65.
21. NICE, *Introduction to health technology evaluation*, in *NICE health technology evaluations:the manual*. 2022.
22. Zellner, A., *An Efficient Method of Estimating Seemingly Unrelated Regressions and Tests for Aggregation Bias.* Journal of the American Statistical Association, 1962. **57**(298): p. 348-&.
23. Hatswell, A.J., et al., *Probabilistic Sensitivity Analysis in Cost-Effectiveness Models: Determining Model Convergence in Cohort Models.* Pharmacoeconomics, 2018. **36**(12): p. 1421-1426.
24. Eckermann, S. and A.R. Willan, *Expected value of information and decision making in HTA.* Health Econ, 2007. **16**(2): p. 195-209.
25. Strong, M., J.E. Oakley, and A. Brennan, *Estimating multiparameter partial expected value of perfect information from a probabilistic sensitivity analysis sample: a nonparametric regression approach.* Med Decis Making, 2014. **34**(3): p. 311-26.