Leeds Institute of Rheumatology and Musculoskeletal Medicine

TEEMS Research Protocol

Version Number 8.0, 15/05/2024

Study Short Title: TEEMS: Targeted treatment Early with Etanercept (biosimilar) plus Methotrexate or methotrexate with T2T care for DMARD-naïve early RA patients - Rationalising treatment based on naïve $CD4^+$ T-cell Stratification.

Full Title: Targeted treatment early with etanercept (biosimilar) plus methotrexate or methotrexate with T2T care for DMARD-naïve early RA patients. A prospective, longitudinal cohort study with an embedded pilot randomised controlled trial to assess treatment rationalisation based on naïve $CD4^+$ T-cell stratification.

Sponsor Name: University of Leeds

Sponsor Number: RR16/209

EudraCT Number: 2016-002344-16

IRAS: 207599

KEY CONTACTS

Chief Investigator:

Professor Paul Emery
T: 0113 39 24883 **E:** p.emery@leeds.ac.uk

Principal Investigator:

Dr Kulveer Mankia
T: 0113 39 24496 **E:** k.s.mankia@leeds.ac.uk

Sub-Investigators:

Dr Hanna Gul
Dr Ai-Lyn Tan
Dr Richard Wakefield
Dr Kate Harnden
Dr Navkiran Doshi
Dr Rahaymin Chowdhury
Dr Leticia Garcia-Montoya
Dr Laurence Duquenne

Trial Coordinator:

T: 0113 39 24734 **E:** leedsth-tr.teems@nhs.net

Site Address:

Leeds Institute of Rheumatology & Musculoskeletal Medicine [LIRMM]
2nd Floor, Chapel Allerton Hospital
Chapeltown Road
Leeds
LS7 4SA

Statistician:

Dr Jianhua Wu
Division of Translational and Applied Health Research,
Faculty of Medicine and Health,
University of Leeds
LS2 9JT
T: 0113 34 33431 **E:** j.h.wu@leeds.ac.uk

Pharmacovigilance Reporting (SAEs/SUSARs):

E: leedsth-tr.sponsorqa@nhs.net

INVESTIGATOR DECLARATION AND SIGNATURE(S)

DECLARATION OF PROTOCOL ACCEPTANCE

I confirm that I am fully informed and aware of the requirements of the protocol and agree to conduct the study as set out in this protocol.

Professor Paul Emery *Chief Investigator*	**Date**

Dr Kulveer Mankia *Principal Investigator*	**Date**

Table of Contents

ABBREVIATIONS

Abbreviation	Term
ACPA	*Anti-citrullinated protein antibody*
AE	*Adverse Event*
ANA	*Anti-nuclear antibody*
CDAI	*Clinical Disease Activity Index*
CF	*Consent Form*
CI	*Chief Investigator*
CRF	*Case Report Form*
CRP	*C-Reactive Protein*
DMARD	*Disease modifying anti-rheumatic drug*
DSUR	*Developmental Safety Update Report*
EAC	*Early Arthritis Clinic*
ETN	*Etanercept*
EMS	*Early Morning Stiffness*
ESR	*Erythrocyte Sedimentation Rate*
FBC	*Full blood count*
GCP	*Good Clinical Practice*
GP	*General Practitioner*
HAQ	*Health Assessment Questionnaire*
HCQ	*Hydroxychloroquine*
IA	*Intra-articular*
ICH	*International Conference On Harmonisation*
IJA	*Independent Joint Assessor*
IM	*Intra-Muscular*
IMP	*Investigational Medicinal Product*
LFT	*Liver function tests*
LIRMM	*Leeds Institute of Rheumatic and Musculoskeletal Medicine*
LOCF	*Last Observation Carried Forward*
LTHT	*Leeds Teaching Hospitals Trust*

Abbreviation	Term
MHRA	*Medicines And Healthcare Products Regulatory Agency*
MRI	*Magnetic Resonance Imaging*
MTX	*Methotrexate*
NIMP	*Non-Investigational Medicinal Product*
OD	*Once Daily*
PI	*Principal Investigator*
PIS	*Patient Information Sheet*
PK/PD	*Pharmacokinetic/ Pharmacodynamic*
PO	*[per os] Oral Administration*
QA	*Quality Assurance*
QoL	*Quality of Life*
RA	*Rheumatoid Arthritis*
RCT	*Randomised Controlled Trial*
RDMS	*Research Data Management System*
REC	*Research Ethics Committee*
RF	*Rheumatoid Factor*
SAE	*Serious Adverse Event*
SC	*Subcutaneous*
SD	*Standard Deviation*
SDAI	*Simplified Disease Activity Index*
SJC	*Swollen Joint Count*
SPC	*Summary Of Product Characteristics*
SSZ	*Sulfasalazine*
SUSAR	*Suspected Unexpected Serious Adverse Reaction*
T2T	*Treat to target*
TJC	*Tender Joint Count*
TNF	*Tumour Necrosis Factor*
U&E	*Urea and Electrolytes*
VAS	*Visual Analogue Scale*

PROTOCOL SYNOPSIS

GENERAL INFORMATION	
Short Title	TEEMS: Targeted treatment Early with Etanercept (biosimilar) plus Methotrexate or methotrexate with T2T care for DMARD-naïve early RA patients - Rationalising treatment based on naïve $CD4^+$ T-cell Stratification.
Full Title	Targeted treatment early with etanercept (biosimilar) plus methotrexate or methotrexate with T2T care for DMARD-naïve early RA patients. A prospective, longitudinal cohort study with an embedded pilot randomised controlled trial to assess treatment rationalisation based on naïve $CD4^+$ T-cell stratification.
Sponsor	University of Leeds
Sponsor ID	RR16/209
EudraCT No.	2016-002344-16
MREC No.	17/YH/0155
Chief Investigator	Professor Emery
Co-ordinating Centre	Chapel Allerton Hospital, Leeds
National / International	National
TRIAL INFORMATION	
Phase	IV
Indication	Early rheumatoid arthritis, remission, targeted treatment
Design	Single centre, phase IV, open-label, prospective, longitudinal cohort study with an embedded pilot randomised controlled trial
Number of sites	1
Primary Objective	• To determine whether the proportion of patients achieving clinical remission after first-line treatment with methotrexate and T2T care differs according to naive $CD4^+$ T-cell frequency (normal/abnormal) at baseline (Arm A vs. Arm B)

Secondary Objective(s)	• To determine the proportion of patients that achieve clinical remission for patients with abnormal baseline naïve $CD4^+$ T-cell frequencies receiving etanercept + methotrexate (Arm C) to obtain preliminary proof-of-concept of superior response compared to methotrexate with T2T care (Arm B) • To determine whether the proportion of patients that achieve imaging remission after first-line treatment with methotrexate differs according to naïve $CD4^+$ T-cell frequency (normal/abnormal) at baseline (Arm A vs. Arm B) • To determine the values of patient-reported outcomes (EMS, VAS scales, HAQ-DI) for patients with abnormal baseline naïve $CD4^+$ T-cell frequencies receiving etanercept + methotrexate (Arm C) to obtain preliminary proof-of-concept of superior response compared to methotrexate with T2T care (Arm B). • To determine whether patient-reported outcomes (, VAS scales, HAQ-DI) after first-line treatment with methotrexate differ according to naïve $CD4^+$ T-cell frequency (normal/abnormal) at baseline (Arm A vs. Arm B) • To determine the proportion of patients that achieve imaging remission for patients with abnormal baseline naïve $CD4^+$ T-cell frequencies receiving etanercept + methotrexate (Arm C) to obtain preliminary proof-of-concept of superior response compared to methotrexate with T2T care (Arm B) • To determine the proportion of patients who normalize their T-cell status for patients with abnormal baseline naïve $CD4^+$ T-cells receiving methotrexate with T2T care or etanercept + methotrexate (Arm B & Arm C) • To determine whether the proportion of patients achieving sustained clinical remission differs between study arms • To determine whether the cumulative amount of corticosteroid use differs between study arms
Primary Endpoint(s)	• The difference in the proportions of patients in clinical remission (DAS28ESR ≤2.6) at 24 weeks of first-line methotrexate with T2T care between those with normal (Arm A) vs. abnormal (Arm B) naïve $CD4^+$ T-cell frequencies

Secondary Endpoint(s)	• The difference in the proportions of patients in clinical remission (DAS28ESR ≤2.6) after 12 weeks of first-line methotrexate with T2T care between those with normal (Arm A) vs. abnormal (Arm B) naïve $CD4^+$ T-cell frequencies • The difference in the proportions of patients in clinical remission (DAS28ESR ≤2.6) at 12 weeks and 24 weeks for patients with abnormal baseline naïve $CD4^+$ T-cell frequencies receiving methotrexate with T2T care (Arm B) vs. etanercept + methotrexate (Arm C) • The differences in the medians of patient-reported outcome measures (EMS, VAS scales, HAQ-DI) after 12 weeks & 24 weeks of first-line methotrexate with T2T care between those with normal (Arm A) vs. abnormal (Arm B) naïve $CD4^+$ T-cell frequencies • The differences in the medians of patient-reported outcome measures (EMS, VAS scales, HAQ-DI) after 12 weeks & 24 weeks for patients with abnormal baseline naïve $CD4^+$ T-cell frequencies receiving methotrexate with T2T care (Arm B) vs. etanercept + methotrexate (Arm C) • The difference in the proportions of patients in imaging remission (PD=0) after 24 weeks of first-line methotrexate with T2T care between those with normal (Arm A) or abnormal (Arm B) naïve $CD4^+$ T-cell frequencies • The difference in the proportions of patients in imaging remission (PD = 0) at 24 weeks for patients with abnormal baseline naïve $CD4^+$ T-cell frequencies receiving methotrexate with T2T care (Arm B) vs. etanercept + methotrexate (Arm C) • The difference in the proportion of patients with normal naïve $CD4^+$ T-cells at 24 weeks for patients with abnormal baseline naïve $CD4^+$ T-cells receiving methotrexate with T2T care (Arm B) vs. etanercept + methotrexate (Arm C) • The difference in the proportions of patients achieving sustained clinical remission (DAS28ESR ≤2.6 at both 12 and 24 weeks) (Arm A vs. Arm B and Arm B vs. Arm C) • The difference in the average (median) cumulative amount of corticosteroid use at 24 weeks between study arms (Arm

	A vs. Arm B and Arm B vs. Arm C). This will include any administered at the 24 week visit.
TRIAL TIMELINES	
Start date	February 2020
Subject enrolment phase	54 months recruitment period (extended from 36 months)
Follow-up duration	24 weeks
End of Trial Definition	When the last patient has completed 24 weeks of follow-up of the trial and any safety data are resolved, procedures are signed off and all analyses of laboratory samples are complete.
Expected completion date	July 2025 (approx.)
TRIAL SUBJECT INFORMATION	
Number of trial subjects	16-30 to be randomised 1:1 to arm B or C, 44-46 to receive standard care in arm A (depending on recruitment rate): total 76-106.
Age group of trial subjects	18 years and older
Inclusion criteria	• Subject has a diagnosis of RA as defined by the new ACR/EULAR 2010 classification criteria • Newly diagnosed (within 12 weeks) • Active disease at screening (DAS28ESR ≥3.2 or clinical evidence of synovitis i.e. at least one swollen joint) • Anti-citrullinated protein antibody (ACPA) positive • Male & female subjects ≥18 years old • DMARD (disease modifying anti-rheumatic drug) naïve • No use of intra-muscular, intra-articular or oral corticosteroids 4 weeks prior to screening • All male and female subjects biologically capable of having children must agree to use a reliable method of contraception for the duration of the study and 24 weeks after the end of the study period. Acceptable methods of contraception are surgical sterilisation, oral, implantable or injectable hormonal methods, intrauterine devices or barrier contraceptives.

	• Patients must have the capacity and be willing to provide written informed consent and comply with the requirements of the protocol • Subjects should be deemed to be in good health with respect to clinical examination and screening blood tests, including full blood count (FBC), urea and electrolytes (U&E), and liver functions tests (LFT) – see exclusion criteria for further details
Exclusion criteria	• Use of any additional investigational medications or products within 4 weeks of screening (including prior to screening) • Use of intra-muscular/intra-articular or oral corticosteroids within 4 weeks prior to screening • Use of more than one NSAID, or increase in dose of NSAIDs within 24 hours before the screening visit. • Live vaccine within <4 weeks prior to screening • Pregnant/lactating women or planning pregnancy within 24 weeks of last protocol treatment • Planned surgery within the study period (requiring omission of study medication > 4 weeks • The presence of other comorbidities, which the physician deems as significant to interfere with evaluation (musculoskeletal condition such as osteoarthritis & fibromyalgia) • Diagnosis of another inflammatory arthritis or connective tissue disease (e.g. psoriatic arthritis or Ankylosing spondylitis, primary Sjögren's syndrome, systemic sclerosis, systemic lupus erythematosus, polymyositis) • Concomitant severe infection requiring intravenous 4 weeks prior to screening • Any contraindication to conventional DMARD's/anti-TNF therapy • Patients with abnormal liver function at the time of screening or abnormal blood tests as shown by: o Aminotransferase (AST) / alanine aminotransferase (ALT) > 3x upper limit of normal (ULN) OR Bilirubin

	> 50µmol/L ○ Serum Creatinine > 175 umol/L ○ eGFR below 30ml/L/min/1.73m^2 ○ neutrophils < 2000 x 10^6/L ○ Platelets < 125 x 10^9/L ○ Haemoglobin < 90 g/L for males and < 85 g/L for females
INVESTIGATIONAL MEDICINAL PRODUCT	
IMP name(s)	Benepali® (Etanercept biosimilar)
IMP mode of administration	Subcutaneous injection as per licenced use (solution for injection in pre-filled pen)
Duration of IMP Treatment	24 weeks
IMP Supplier(s)	Samsung Bioepis
Non IMP name(s)	• Methotrexate (MTX) • Hydroxychloroquine (HCQ) • Sulfasalazine (SSZ) • Folic Acid (FA) • Intra-muscular/Intra-articular methylprednisolone (Depo-Medrone) or triamcinolone (Kenalog) • Oral prednisolone

1. INTRODUCTION

- Rheumatoid arthritis (RA) is a chronic inflammatory disease which, if untreated can lead to significant disability and poor quality of life (QoL).
- Treatment with disease modifying anti-rheumatic drugs (DMARD's), including biologic therapies significantly improves outcomes.
- The current aim of treatment in RA is remission and the current optimal treatment approach is to start methotrexate (MTX) therapy early.
- Different medications for RA have shown varying success in inducing and maintaining remission.
- Biologic medications are expensive and may be associated with potential serious side effects and high costs. Furthermore, long-term outcomes are unknown.
- Our previous research has demonstrated that T-cell phenotyping at baseline could predict remission in DMARD-naïve early RA patients treated with MTX.
- Prediction of MTX therapy response remains a key clinical need to enable the identification of patients who would benefit from an alternative, more aggressive treatment strategy**.**

This study aims to assess the clinical utility of T-cell stratification for rationalising treatment with MTX, therefore enabling early targeted treatment for those with a poorer prognosis based on their immunological status.

1.1. Background

RA is a chronic systemic autoimmune disease characterised by a symmetrical inflammatory polyarthropathy. Inflammation of the synovial lining (synovitis) is responsible for triggering structural joint damage which, if untreated can lead to significant physical disability and reduced quality of life (QoL)[1, 2]. The Incidence of RA is approximately 0.5-1% with 5-50 per 100000 adults in developed countries[3].

As there is no known cure for RA, the key therapeutic target is to suppress inflammation and prevent any deterioration in joint damage and function, thus achieving a state of remission[4]. The approach to treating RA has witnessed dramatic changes over recent years. With the advent biologic therapies and treat to target strategies, rates of clinical remission have significantly improved, making it an achievable goal[2, 5]. The European League Against Rheumatism (EULAR) has stated it as their primary treatment goal[6].

The current optimal therapeutic approach in early RA is to start MTX to target inflammation and induce remission[7]. Prediction of MTX therapy response remains a key clinical need to enable the identification of patients who would benefit from an alternative, more aggressive treatment strategy. Multiple predictors of remission with MTX have been reported over the years[8-15], reviewed in[2], but none have entered routine clinical practice.

We previously reported that T-cell phenotyping at baseline could predict remission in DMARD-naïve early RA treated with MTX. Reduced naïve T-cell frequency was the most predictive factor, using both a pilot[16] and a replication cohort (Ponchel 2015, submitted). Sensitivity/specificity at 79%/81% and a positive predictive value (PPV)/negative predictive value (NPV) at 78%/81% were reported with an odd ration of 15 for the achievement of remission (submitted). Despite small patient numbers in both the original study (n=50) and in the replication set (n=70), these data confirmed the potential value of using naïve CD4+ T-cell as a biomarker of MTX induced remission in early RA. The clinical utility of measuring T-cell subsets is therefore strongly indicated by these data and suggests that measurement of T-cell subsets can rationalise the use of MTX as first-line therapy.

In our pilot study, the association between lower naïve T-cells and the inability to achieve remission was not observed in patients treated with combination therapy MTX + anti-TNF[16]. It may therefore be appropriate to consider biologics early in patients with poor prognostic naïve CD4+ T-cells. The current proposal aims to confirm the clinical value of T-cell subset quantification for the prediction of MTX response in early RA, by stratified interventions based on naïve CD4+ T-cell status.

1.2 Investigational medicinal product (IMP)

Within the trial, the following is classed as an Investigational Medicinal Product (IMP):

- ***Benepali®:***
    - Etanercept biosimilar
    - Administered subcutaneously (sc) 50mg/week
    - In combination with MTX is indicated for the treatment of moderate to severe active RA in adults when the response to disease-modifying anti-rheumatic drugs, including MTX (unless contraindicated), has been inadequate
    - Can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate
    - Also indicated in the treatment of severe, active and progressive RA in adults not previously treated with MTX
    - Has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function (alone or in combination with MTX)[17]

1.2.1. Summary of product characteristics (SPC)

- The SPC for Benepali® will be used in this study.

1.2.2. Non IMP(s)

1.2.2.1. Conventional DMARDs

- ***MTX:***
    - Licenced in RA, often as first-line therapy.
- ***Hydroxychloroquine (HCQ)***:
    - Licenced in RA, often a second-line therapy. Can be used in combination with MTX and Sulfasalazine or monotherapy for mild disease.
- ***Sulfasalazine (SSZ):***
    - Licenced in RA, often a second-line therapy. Can be used in combination with MTX and HCQ or monotherapy for patients intolerant to MTX.

1.2.2.2 Supportive medication

Folic Acid: Patients taking MTX will be co-prescribed oral folic acid as per standard care in our T2T clinic (5mg daily, 6 days per week, except day of MTX).

Administration of IMP' & non-IMPs:

- For patients with normal baseline naïve $CD4^+$ T-cells (Arm A), MTX will be administered as per standard T2T care at a starting dose of 15mg/week PO*. If tolerated, dose escalation will occur at follow-up in line with our T2T schedule.
- Patients with abnormal baseline naïve $CD4^+$ T-cells will be randomized to receive either MTX 15mg/week PO* (Arm B) or MTX 15mg/week PO* + Benepali® 50mg SC injection, as per licenced use (Arm C). Follow-up of patients in both arms and dose escalation of MTX will also occur in line with our T2T schedule.
- The treating physician will have been monitoring patients for side effects from the beginning of their treatment. Side effects will be monitored by clinical assessment and by blood testing at each study visit.

  **(or SC as per standard practice – see section 7.3 for further guidance)*

Rescue medication/treatment of flare

- Patients in either study arm may receive corticosteroid treatment (IM/IA or oral) at any of the follow-up study visits or at unscheduled visits if they have evidence of clinical flare i.e. do not meet target DAS28ESR<2.6. Administered doses will be in line with local standard clinical practice. For patients meeting the target DAS score, however have evidence of flare i.e. synovitis as per the assessing physician, corticosteroids may be offered. Administration of this will be logged in the CRF.
- Small doses of corticosteroids are relatively safe, with only a small risk of side effects e.g. weight gain, mood and sleep disturbance, which are usually only short-lived.
- Long-term use of high doses is often associated with bone loss and worsening of osteoporosis. Rarely avascular necrosis can occur. Corticosteroids can also transiently cause an increase in blood sugars, necessitating increased blood sugar monitoring/extra caution in diabetic patients. Menstrual disturbance has also been noted.
- Injections can occasionally cause thinning of the skin or depigmentation at the injection site. Intra-articular injections may be associated with increased pain within the joint for 24 hours and rarely joint infection in less than 1:5000 cases. The need for rescue medication will be recorded as an adverse event.

1.3. Rationale for the proposed study

- The current optimal therapeutic approach in early RA is to start MTX to target inflammation and induce remission.
- Prediction of MTX therapy response remains a key clinical need to enable the identification of patients who would benefit from an alternative, more aggressive treatment strategy. Multiple predictors of remission with MTX have been reported over the years but none have entered routine clinical practice.
- We previously reported that T-cell phenotyping at baseline could predict remission in DMARD-naïve early RA treated with MTX. Reduced naïve $CD4^+$ T-cell frequency was the most predictive factor, using both a pilot and a replication cohort.
- These data confirmed the potential value of using naïve $CD4^+$ T-cells as a biomarker of MTX induced remission in early RA. The clinical utility of measuring T-cell subsets is therefore strongly indicated by these data and suggests that measurement of T- cell subsets can be used to rationalise the use of MTX as first-line therapy.
- Predicting response to MTX has important clinical value to identify patients who will do well on MTX but furthermore for directing those who will have a sub-optimal response to MTX to receive alternative therapy without any harmful delay and in line with the treat to target principle.
- The current proposal aims to confirm/validate the clinical value of T-cell subset quantification for the prediction of MTX response in early RA, by stratified interventions based on baseline naïve $CD4^+$ T-cell status.

2. STUDY AIM AND OBJECTIVES

2.1. Study aim

- To determine whether the use of MTX as a first-line agent can be rationalised based on baseline naïve $CD4^+$ T-cell stratification in DMARD-naïve early RA patients.

2.2. Research Hypothesis

- A greater proportion of patients with normal naïve $CD4^+$ T-cell frequencies for their age (Arm A) will achieve clinical remission after 24 weeks of first-line therapy with MTX and T2T care compared to those with abnormally low naïve $CD4^+$ T-cell frequencies (Arm B).

2.3. Primary Objective

- To determine whether the proportion of patients achieving clinical remission after first-line treatment with MTX and T2T care differs according to naive $CD4^+$ T-cell frequency (normal/abnormal) at baseline (Arm A vs. Arm B).

2.4. Secondary objective(s)

- To determine the proportion of patients that achieve clinical remission for patients with abnormal baseline naïve $CD4^+$ T-cell frequencies receiving etanercept + MTX (Arm C) to obtain preliminary proof-of-concept of superior response compared to MTX with T2T care (Arm B).
- To determine whether the proportion of patients that achieve imaging remission after first-line treatment with MTX differs according to naïve $CD4^+$ T-cell frequency (normal/abnormal) at baseline (Arm A vs. Arm B).
- To determine the values of patient-reported outcomes (EMS, VAS scales, HAQ-DI) for patients with abnormal baseline naïve $CD4^+$ T-cell frequencies receiving etanercept + MTX (Arm C) to obtain preliminary proof-of-concept of superior response compared to MTX with T2T care (Arm B).
- To determine whether patient-reported outcomes (EMS, VAS scales, HAQ-DI) after first-line treatment with MTX differ according to naïve $CD4^+$ T-cell frequency (normal/abnormal) at baseline (Arm A vs. Arm B).
- To determine the proportion of patients that achieve imaging remission for patients with abnormal baseline naïve $CD4^+$ T-cell frequencies receiving etanercept + MTX (Arm C) to obtain preliminary proof-of-concept of superior response compared to MTX with T2T care (Arm B).
- To determine the proportion of patients who normalize their T-cell status for patients with abnormal baseline naïve $CD4^+$ T-cells receiving MTX with T2T care or etanercept + MTX (Arm B & Arm C).
- To determine whether the proportion of patients achieving sustained clinical remission differs between study arms
- To determine whether the cumulative amount of corticosteroid use differs between study arms

3. STUDY ENDPOINTS

3.1 Primary endpoint

- The difference in the proportions of patients in clinical remission (DAS28ESR ≤2.6) after 24 weeks of first-line MTX with T2T care between those with normal (Arm A) vs. abnormal (Arm B) naïve $CD4^+$ T-cell frequencies. Those with T-cell frequencies at or above the level expected for their age will be considered to have normal levels; those whose levels are lower than expected for their age will be considered to have abnormal levels.

3.2. Secondary endpoint(s)

- The difference in the proportions of patients in clinical remission (DAS28ESR ≤2.6) after 12 weeks of first-line MTX with T2T care between those with normal (Arm A) vs. abnormal (Arm B) naïve $CD4^+$ T-cell frequencies.
- The difference in the proportions of patients in clinical remission (DAS28ESR ≤2.6) at 12 & 24 weeks for patients with abnormal baseline naïve $CD4^+$ T-cell frequencies receiving MTX with T2T care (Arm B) vs. etanercept + MTX (Arm C).
- The differences in the medians of patient-reported outcome measures (EMS, VAS scales, HAQ-DI) after 12 & 24 weeks of first-line MTX with T2T care between those with normal (Arm A) vs. abnormal (Arm B) naïve $CD4^+$ T-cell frequencies.
- The differences in the medians of patient-reported outcome measures (EMS, VAS scales, HAQ-DI) after 12 & 24 weeks for patients with abnormal baseline naïve $CD4^+$ T-cell frequencies receiving MTX with T2T care (Arm B) vs. etanercept + MTX (Arm C).
- The difference in the proportions of patients in imaging remission (PD=0) after 24 weeks of first-line MTX with T2T care between those with normal (Arm A) or abnormal (Arm B) naïve $CD4^+$ T-cell frequencies.
- The difference in the proportions of patients in imaging remission (PD=0) at 24 weeks for patients with abnormal baseline naïve $CD4^+$ T-cell frequencies receiving MTX with T2T care (Arm B) vs. etanercept + MTX (Arm C).
- The difference in the proportion of patients with normal naïve $CD4^+$ T-cells at 24 weeks for patients with abnormal baseline naïve $CD4^+$ T-cells receiving MTX with T2T care (Arm B) vs. etanercept + MTX (Arm C).
- The difference in the proportions of patients in sustained clinical remission (DAS28ESR ≤2.6) at both 12 and 24 weeks (Arm A vs. Arm B and Arm B vs. Arm C)

- The difference in the average (mean) amount of corticosteroid use at 24 weeks between study arms (Arm A vs. Arm B and Arm B vs. Arm C). This includes any administered at the 24 week visit also.

4. STUDY VARIABLES

4.1. Standard variables

- Age (years)
- Gender (male/female)
- Concomitant medications/allergy history
- Surgical/medical history
- Family history
- Smoking history
- Anti-citrullinated protein antibody (ACPA) titre and status (positive/negative)
- Rheumatoid factor antibody (RF) titre and status (positive/negative)
- Anti-nuclear antibody (ANA) titre and status (positive/negative)
- Date of RA diagnosis

4.2. Efficacy variables

- Tender joint count (range 0-28)
- Swollen joint count (range 0-28)
- Erythrocyte sedimentation rate (mm/hr)
- C-reactive protein (mg/L)
- DAS28 disease activity (derived; range 0-10)
- CDAI disease activity (derived; range 0-76)
- SDAI disease activity (derived; range 0-86)
- ACR/Boolean remission status (derived; yes/no)
- Physician global assessment VAS (mm; range 0-100)
- Early morning stiffness (EMS) (mins; range 0-720)
- Patient general health VAS (mm; range 0-100)
- Patient assessment of disease activity VAS (mm; range 0-100)
- Patient assessment of pain VAS (mm; range 0-100)

- Health Assessment Questionnaire Disability Index (HAQ-DI) (range 0-3)
- Number of joints scoring PD>0 (range 0-13 bilaterally), and tendons (range 0-5 bilaterally)
- Number of joints scoring GS>1 (range 0-13 bilaterally), and tendons (range 0-5 bilaterally)
- Naïve T-cell frequency (%)

4.3. Exploratory biomarkers

Serum and plasma samples collected at baseline and at Week 24 will also be stored (for future evaluation of disease categorization, auto-antibodies, inflammatory, immunological and vascular biomarkers and products of synovial, cartilage and bone turnover in this and future studies (subject to ethical review of such studies)).

A maximum of 40ml of blood will be drawn at each relevant visit. This will be collected, processed and stored in accordance with local practice.

4.4. Safety variables

- Number of patients experiencing SAEs and AEs.
- Any clinically significant worsening of a pre-existing condition.
- An AE occurring from overdose of an IMP, whether accidental or intentional.
- An AE occurring from abuse (e.g. use for non-clinical reasons) of an IMP
- An AE that has been associated with the discontinuation of the use of an IMP

5. STUDY DESIGN

Schematic/Timeline

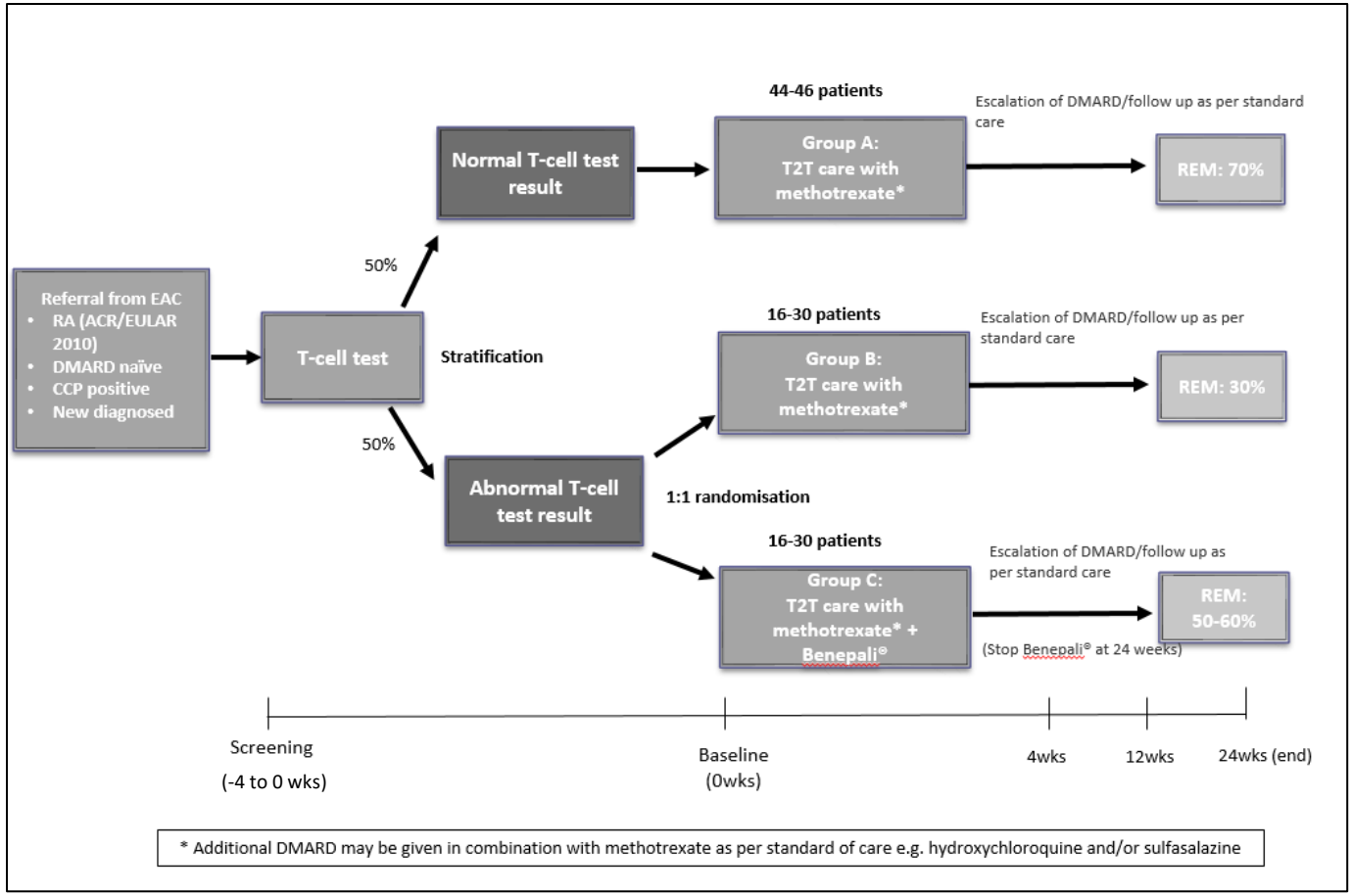

Figure 1: Schematic showing study timeline, interventions and expected proportions of remission in each study arm.

5.1. Study description

- This is a Single centre, phase IV, open-label, prospective, longitudinal cohort study with an embedded pilot randomised controlled trial that aims to assess whether MTX can be rationalised as a first-line treatment for DMARD-naïve early RA patients, according to baseline naïve $CD4^+$ T-cell stratification.

- Patients with newly diagnosed RA satisfying the following inclusion criteria will be recruited from our early arthritis clinic:
    - Subject has a diagnosis of RA as defined by the new ACR/EULAR 2010 classification criteria
    - Newly diagnosed (within 12 weeks)
    - Presence of anti-citrullinated peptide antibody (ACPA)
    - DMARD-naïve
    - Active disease (DAS28ESR ≥3.2 or clinical evidence of synovitis i.e. at least one swollen joint)

- Eligible patients will be provided with written information on the study and will be given a minimum of 24 hours to read this information prior to being contacted by a research nurse (within one week). If interested they will be invited to a screening appointment within four weeks to confirm eligibility, obtain written consent and to collect the necessary clinical and laboratory data as per the study schedule. Following the screening visit, patients will attend a baseline assessment within four weeks.

- Patients will be stratified based on their naïve $CD4^+$ T-cell frequency (normal or abnormal based on our pre-defined cut-off values according to age and sex-matched controls).

- Patients with a normal T-cell frequency (Arm A) will commence MTX 15mg/week PO* as per standard T2T practice. Follow-up (4, 12 and 24 weeks), dose escalation of MTX and treatment of flare will also be conducted in line with T2T care.

- Patients with an abnormal T-cell frequency will be randomized 1:1 into 2 groups using randomly permuted block sizes (see section 6.5.3. for further details) and also followed up as per T2T care:

- The first group (Arm B) will receive MTX 15mg/week PO*
- The second group (Arm C) will receive MTX 15mg/week PO* in combination with 50 mg subcutaneous Benepali® administered weekly.

  **(or SC as per standard practice – see section 7.3 for further guidance)*

- Patients will be followed up for a period of 24 weeks and will undergo clinical, immunological and imaging assessments as stated in the study schedule. Following completion of the study, patients will either be followed up in our established inflammatory arthritis or biologics clinic. Patients in group C will discontinue their Benepali®.

- This study will take place at the rheumatology out-patient department in Chapel Allerton Hospital, Leeds.

5.2. Study Duration

- The total duration of the study for patients completing all visits from screening to final assessment will be 28 weeks maximum (up to 4 weeks between screening and baseline visit).

- The study will run for an estimated period of approximately 5.5 years from the start date: including the recruitment period, length of trial and time needed for all analyses and use of samples. Due to the nature of clinical trials this time period may vary.

5.3. Rationale for study design and selection of dose

- Based on our previous data from both a pilot study and replication cohort, it was observed that reduced naïve $CD4^+$ T-cells at baseline could predict remission in DMARD-naïve early RA patients treated with MTX. The association between lower naïve CD4+T-cells and inability to achieve remission was not observed for patients treated with combination MTX + anti-TNF. Therefore, it may be appropriate to consider biologic therapy early in patients with poor prognostic naïve $CD4^+$ T-cells. This data suggests that the measurement of T-cell subsets is strongly indicated in clinical practice to facilitate earlier, more targeted treatment [16].
- Subsequently we aimed to conduct a prospective, longitudinal cohort study with an embedded pilot randomised controlled trial to investigate this. An open-label design has been chosen as creation and administration of a placebo is not feasible for this study.

- Methotrexate initiation at 15mg and escalation to 25mg is in line with the standard of care/T2T practice in Leeds. Depo-medrone 120mg injection IM is the standard dose used in Leeds and represents a pragmatic approach to induce rapid suppression of inflammation however, alternative doses, agents and routes of administration may be used as an alternative, as previously described.

- Current product licensing recommends a dose of 50mg/wk subcutaneously for Benepali®.

6. SELECTION AND WITHDRAWAL OF SUBJECTS

6.1. Target population

- Patients with a new diagnosis of RA (within 12 weeks) as defined by the new ACR/EULAR 2010 criteria. Patients must be ACPA positive and treatment (DMARD) - naïve.

6.2. Estimated number of eligible participants

- Based on the recruitment rates of similar studies within the department, we anticipate being able to recruit a minimum of 76 patients within 2 years.

6.3. Eligibility criteria

6.3.1 Inclusion criteria

1. Subject has a diagnosis of RA fulfilling the new ACR/EULAR 2010 classification criteria
2. Newly diagnosed (within 12 weeks)
3. Active disease (clinical evidence of synovitis i.e. at least one swollen joint or DAS28ESR >3.2)
4. ACPA positive
5. Male & female subjects ≥18 years old.
6. DMARD-naïve
7. No use of intra-muscular/Intra-articular or oral corticosteroids 4 weeks prior to screening.
8. All male and female subjects biologically capable of having children must agree to use a reliable method of contraception for the duration of the study and 24 weeks after the end of the study period. Acceptable methods of contraception are

surgical sterilisation, oral, implantable or injectable hormonal methods, intrauterine devices or barrier contraceptives.

9. Patients must have the capacity and be willing to provide written informed consent and comply with the requirements of the protocol.
10. Subjects must be deemed to be in good health with respect to clinical examination and screening blood tests, including FBC, U&E and LFT tests.

6.3.2 Exclusion Criteria

General

1. Use of any additional investigational medicinal products within 4 weeks of screening.
2. Use of IM/IA or oral corticosteroids within 4 weeks prior to screening.
3. Use of more than one NSAID, or increase in dose of NSAID within 24 hours of the screening visit.
4. Planned surgery within the study period (requiring omission of study medication > 4 weeks).
5. The presence of other comorbidities (including MSK conditions such as OA & fibromyalgia), which the physician deems as significant to interfere with evaluation of RA.
6. Diagnosis of another inflammatory arthritis or CTD (e.g. psoriatic arthritis or ankylosing spondylitis, primary Sjögren's syndrome, systemic sclerosis, systemic lupus erythematosus, polymyositis).

6.3.3 Exclusions for general safety

- Contraindications to anti-TNF as determined by local prescribing guidelines and physician discretion, including:

1. Patients with significant concurrent medical diseases including but not limited to uncompensated congestive heart failure, myocardial infarction within 52 weeks from screening, unstable angina pectoris, uncontrolled hypertension (BP>160/95), severe pulmonary disease, or history of human immunodeficiency virus (HIV) infection, immunodeficiency syndromes, central nervous system (CNS) demyelinating events suggestive of multiple sclerosis, renal or gastrointestinal conditions, which in the opinion of the investigator places the patient at an unacceptable risk for participation in the study or would make implementation of the protocol difficult.

2. Patients with cancer or a history of cancer (other than resected cutaneous basal cell carcinoma, and in situ cervical cancer) within 5 years of screening.

3. Patients with current infective arthritis.

4. Patients with chronic infection of the upper respiratory tract (eg. Sinusitis), chest (eg. bronchiectatic lung disease), urinary tract or skin (eg. Paronychia, chronic ulcers, open wounds) within 4 weeks of screening.

5. Patients who have a chest radiograph within 24 weeks prior to the first administration of study agent that shows an abnormality suggestive of a malignancy or current active infection, including TB, histoplasmosis or coccidioidomycosis.

6. Patients with any ongoing or active infection or any major episode of infection requiring hospitalization or treatment with IV antibiotics within the preceding 4 weeks of screening and/or orally administered antibiotics in the preceding 2 weeks of screening.

7. Patients with a history of latent or active TB prior to screening will not be eligible.

8. Subjects must undergo screening for hepatitis B and C viruses .At a minimum, this includes testing for HBsAg (surface antigen anti-HBc total (core antibody total) and anti-HCV antibody.

    a. Subjects who test positive for surface antigen (HBsAg+) are not eligible for this study, regardless of the results of other hepatitis B tests.

    b. Subjects who test negative for surface antigen (HBsAg-) and positive only for core antibody (anti-HBc+) must undergo further testing for hepatitis B deoxyribonucleic acid (HBV DNA test). If the HBV DNA test is positive, the subject is not eligible for this study. If the HBV DNA test is negative, the subject is eligible for this study. In the event the DNA test cannot be performed, the subject is not eligible for the study.

    c. Patients who test positive for anti-HCV antibody are not eligible for this study.

    d. Primary or secondary immunodeficiency (history of or currently active) unless related to primary disease under investigation.

    e. Patients must be screened for the Human Immunodeficiency Virus (HIV).

If positive, the subject is not eligible for the study.

Other exclusions for safety:

- Patients with abnormal liver function at the time of screening or abnormal blood tests as shown by:
    - Aminotransferase (AST) / alanine aminotransferase (ALT) > 3x upper limit of normal (ULN) OR Bilirubin >51µmol/L
- Patients with known severe hypoproteinaemia at the time of screening, e.g. in nephrotic syndrome or impaired renal function, as shown by:
    - Serum Creatinine ≥175 µmol/L
    - eGFR below 30ml/L/min/1.73m^2
- Patients with known significantly impaired bone marrow function as for example significant anaemia, leukopaenia, neutropaenia or thrombocytopaenia as shown by the following laboratory values at the time of screening:
    - Neutrophils < 2000 x 10^6/L
    - Platelets < 125 x 10^9/L
    - Haemoglobin < 90 g/L for males and < 85 g/L for females
- Pregnancy (including planning pregnancy within 24 weeks of last protocol treatment), lactation (nursing) or women of child-bearing potential (WCBP) unwilling to use an effective birth control measure (see 6.3.1)
- Patients with a history of confirmed blood dyscrasia.
- Patients with a history of any viral hepatitis within 1 year of screening
- Patients who have received or are expected to receive any live virus or bacterial vaccinations or treatments that include live organisms (e.g. a therapeutic infectious agent such as BCG that is instilled into the bladder for the treatment of cancer) within 3 months prior to the first administration of study agent, during the trial, or within 6 months after the last administration of the study agent.

- Planned surgery within the study period (requiring omission of study medication >4 weeks).
- Patient in receipt of live vaccine <4 weeks prior to screening

6.3.4. Screening Failures

Participants who sign an informed consent form and fail to meet the inclusion and/or exclusion criteria are defined as screen failures. For all screen failures, the investigator is to maintain a screen log that documents the screening number, participant initials, and reason(s) for screen failure. A copy of the log should be retained in the investigator's study files.

6.4. Treatment withdrawal criteria

Patients **MUST** be withdrawn from the study **treatment** if any of the following occur:

- Pregnancy
- Serious adverse event (SAE) related to the study treatment
- Serious infection requiring IV antibiotics
- Development of blood dyscrasia, malignancy or demyelinating disorder
- Major surgical intervention
- Withdrawal of consent
- Chief or Principal Investigator decision
- Sponsor decision
- Poor patient compliance with study protocol (< 80% attendance of study visits)
- Poor patient compliance with study treatments (basic assessment/history in clinic/diary cards for Benepali)
- Omission of treatment > 4 weeks
- Transaminase raise > 3 x ULN
- Serum creatinine >175 μmol/L /eGFR below 30ml/L/min/1.73m^2

Patients withdrawn from treatment will continue to be followed using the eCRFs for the duration of the study.

Patients will be **FULLY** withdrawn from the study only if they request so. Please, see section 6.5.5.

6.5. Recruitment, consent and randomisation processes

6.5.1. Eligibility screening and recruitment

Eligibility screening

- All participants screened for eligibility for the trial, including those who go on to be randomized, will be included on the trial-specific screening log. Anonymized information will be collected including:
    - Age
    - Gender
    - Ethnicity
    - Date screened
    - Randomised/Not randomised. If not randomised, reason for non-randomisation:
        - Not eligible for trial participation and reason for this, or
        - Eligible but declined and reason for this, or
        - Other reason for non-randomisation. This information will be collected and reviewed on a monthly basis throughout the trial.

Recruitment & Informed consent

- Patients will be approached in the early arthritis clinic at Chapel Allerton Hospital during routine appointments (either face-to-face or telephone) and will be provided with verbal and written details about the trial. A verbal explanation of the trial together with the Patient Information Sheet (PIS) and Consent Form (CF) will be provided by the patient's clinical team (medical and nursing). **The PIS may be sent via post or secure email, where the initial patient contact and approach was made via a telephone clinic.** This PIS will include detailed information about the rationale, design and personal implications of the trial.

  Following information provision, patients will have as long as they need to consider participation (a minimum of 24 hours is advised) and will be given the opportunity to discuss the trial with their family and other healthcare professionals before they are

asked whether they would be willing to participate.

- It is anticipated that a member of the research team will contact patients within 1 week. If willing to participate, they will be invited to meet a healthcare professional (HCP) if they wish to discuss further. Provision of the PIS and willingness to participate in the study will be documented in the notes.

6.5.2. Consent

- Willing patients will be formally assessed in clinic for eligibility and invited to provide informed, written consent. The eligibility decision will be recorded by a clinician delegated to do so and will be recorded in the patients notes and in the CRF. The Chief Investigator, Principal Investigator or any other clinically qualified member of the trial team who has received Good Clinical Practice (GCP) training and is authorised on the trial delegation log, are permitted to take informed consent.
- Where the patient is able to provide fully informed consent but is unable to sign or otherwise mark the consent form, provision for completion of the consent form by a witness will be made. This should be a carer, friend/family member, or a local member of the clinical team who is independent of the research team.
- Where English is not the patient's first language every effort will be made to provide a Trust interpreter according to normal Trust procedures.
- The right of the patient to refuse consent without giving reasons will be respected. Further, the patient will remain free to withdraw from the study at any time without giving reasons and without prejudicing any further treatment.
- A record of the consent process detailing the date of consent and all those present will be kept in the patient's notes. The original CF will be retained in the Trial Master File (TMF), a copy of the CF will be given to the patient and a second copy filed in the hospital notes (as per local practice).
- Where valid, informed consent is obtained from the patient and the patient subsequently becomes unable to give informed consent by virtue of physical or mental incapacity, the consent previously given when capable remains legally valid. Patients who lose capacity after informed consent has been obtained will continue with protocol treatment and follow- up at the discretion of the treating investigator.

6.5.3. Randomisation process

- Patients with abnormal baseline naïve $CD4^+$ T-cells will be randomised 1:1 and receive MTX with T2T care vs. Benepali® + MTX.

- The pharmacy at Chapel Allerton Hospital will prepare a randomisation schedule. A central randomisation method using randomly permuted block sizes will be used. The Trials team at Leeds General Infirmary will hold the master randomisation list and, as patients enter the study, they will be assigned the next available Patient ID Number and assigned to receive treatment with either MTX + Benepali® or MTX with T2T care.

- Informed written consent for entry into the trial must be obtained prior to randomisation, subject to the patient meeting the eligibility criteria. Randomization should take place as soon as possible after consent is obtained and T-cell status is known and must be performed by an authorized member of the clinical team at the site using the LTHT Pharmacy telephone randomisation service.

- The following information is required in order for the patient to be randomized. The person making the randomization telephone call should have all details to hand:

    - Patient initials and date of birth

    - Name of person undertaking randomisation

    - Name of the treating investigator

    - Confirmation of eligibility

    - Confirmation of written informed consent and date

    - T-cell status

    - Confirmation that screening clinical data has been collected

- A unique trial patient identifier will be assigned at randomization. After randomization the research site will:

    - Ensure that patients are notified of their appointment dates. Notify the patients' GP of their participation in the trial via formal letter.

    - Following patient randomisation, the authorised person performing the randomisation must complete the Patient Randomisation form. The Patient Randomisation form will contain the patient's details (initials, date of birth, trial number) and the date of randomisation. LTHT Pharmacy will also complete a Patient Randomisation form. The Patient Randomisation form

completed by PTHT Pharmacy will contain the patient's details (initials, date of birth, trial number), the date of randomisation and treatment allocation.

6.5.4. Study blinding

- Patients will not be blinded to treatment. Patients will not be told their T-cell result however, those randomised to receive Benepali® will know they will have abnormal T-cell subsets as this will be outlined in the PIS.
- Clinicians will not be blinded to treatment or T-cell result, however the joint count will be conducted independently by a suitably qualified and competent individual (as an independent joint assessor [IJA]) to minimise bias. This individual will not be involved in patient care and will be instructed not to discuss disease activity or treatment with patients or Principal Investigator.
- Ultrasound scans will be performed by sonographers blind to treatment allocation and T-cell result; patients will be instructed not to discuss details of their treatment during their scan.
- Randomisation codes will remain blinded to clinicians recruiting to the study as these will be administered centrally.

6.5.5. Patients who withdraw consent

- When a subject discontinues or withdraws consent the investigator will notify the sponsor. The reason will be documented in the subject's record.
- Patients can withdraw their consent at any time-point within the study.
- An effort must be made to determine why a subject fails to return for the necessary visits. This information should be recorded in the subject's record.
- Unless the patient specifically withdraws consent for their data to be stored, all data and samples collected from them will continue to be stored as per the original patient consent.

6.5.6. Managing/replacing patients who withdraw early

- Patients who withdraw early from study will be followed up in line with standard NHS care (T2T).
- Patients who withdraw from the trial early will not be replaced.

6.5.7. Definition for the end of the trial

- The trial will end when all participants have completed 24 weeks of follow-up of the trial, any safety data are resolved and procedures are signed off and when analysis of study samples is complete.

7. STUDY TREATMENTS

7.1. General information on the products (trial drugs) to be used

Within the trial, the following is classed as an Investigational Medicinal Products (IMP):

- **Benepali®:** In combination with MTX is indicated for the treatment of moderate to severe active RA in adults when the response to disease-modifying anti-rheumatic drugs, including MTX (unless contraindicated), has been inadequate.
    - Can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate.
    - Also indicated in the treatment of severe, active and progressive RA in adults not previously treated with MTX.
    - Has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function (alone or in combination with MTX)[17].

MTX in a non-IMP as it is not being used in this study outside its licensed use. It is used as a first-line therapy for RA. Similarly, hydroxychloroquine (HCQ), sulfasalazine (SSZ) and folic acid (FA) are non-IMPs.

7.2. Frequency and duration of the trial drugs

For patients with normal baseline naïve $CD4^+$ T-cells (Arm A), MTX, 15mg/week PO* will be the first-line treatment. Escalation of treatment and treatment of flare will be in-line with standard T2T care.

Patients with abnormal baseline naïve $CD4^+$ T-cells will be randomized 1:1 to receive either MTX 15mg/week PO* with T2T care (Arm B) or MTX (15mg/week PO*) + Benepali®, administered according to its licensed use, 50mg s/c weekly (Arm C).

At the end of the trial, patients in the combination therapy group will discontinue Benepali®. If this is not tolerated during the study, patients will follow the standard T2T pathway with conventional DMARD therapy (as per arms A&B).

**(or SC as per standard practice – see section 7.3 for further guidance)*

7.3. Administration/handling of the trial drugs

- MTX: Oral preparation or (e.g. for participants experiencing GI side effects) subcutaneously in line with standard of care, patients self-administer at home as per standard care.
- HCQ: Oral preparation, patients self-administer at home as per standard care.
- SSZ: Oral preparation, patients self-administer at home as per standard care.
- FA: Oral preparation, patients self-administer at home as per standard care.
- Benepali®: Subcutaneous preparation (pen), patients self-administer at home. Patients will be taught how to administer the injections by a clinical nurse specialist.

7.3.1. Handling, storage and supply

Study drug(s) will be delivered to pharmacy and labelled according to the terms of the MHRA approval. This study will aim to reflect normal practice as much as possible, so dispensing and IMP management will reflect this whilst adhering to regulations.

IMP Formulation and storage

Formulation and storage of IMP will be in line with the manufacturers' recommendations. For further details refer to the SmPC for Benepali. A reference copy can be found in the Investigator Site Files.

IMP Preparation

All IMPs will be prepared and handled in line with manufacturers' recommendations.

IMP Labelling and handling

MTX will be off an off-the shelf supply. There is no requirement to ring-fence off the shelf general hospital supplies of this. Pharmacy will be responsible for labelling the IMP in accordance with the requirements of the Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994. Pharmacy will record batch numbers on the Trial Prescription Form and identify the request as a trial drug.

IMP Prescribing and administration

All drugs will be administered to eligible patients under the supervision of the Principal Investigator or identified sub-investigator(s). For all treatment regimens, dose capping based

on out-of-range BSA and alterations in drug scheduling (due to holidays etc.) is at the discretion of the local Principal Investigator. Patients will be treated on an outpatient basis.

7.3.2 Drug accountability

The pharmacies will maintain a log of drug accountability for each participant. The research staff will record study medication doses and compliance in the CRF at each visit.

7.3.3 Blood monitoring for trial drugs

Patients will have blood monitoring for DMARDSs in accordance with standard of care and the patient's particular clinical situation. Investigators will monitor these, and it will be at their discretion to contact the patient and or GP regarding any missing blood tests. Stopping/switching treatment based on blood test results will be at the discretion of the treating study physician and recorded in the CRF.

7.4 Prior and concomitant illness

Additional illnesses present at the time informed consent is obtained are regarded as concomitant illnesses and must be documented in the case report form (CRF).

Relevant past illnesses must also be documented in the CRF.

Please see inclusion/exclusion criteria.

7.5 Prior and concomitant medications

7.5.1. Permitted prior medications

All treatments being taken by the participants on entry to the trial or at any time during the trial, in addition to the investigational medicinal product are regarded as concomitant treatments and must be documented in the participant's hospital notes and recorded on the Medication sections of the CRF.

New use of steroid treatment such as oral steroids or intra-muscular or intra-articular methylprednisolone will count as intervention, and will be recorded.

7.5.2. Prohibited prior medications

Steroid use, experimental drugs and live vaccines within 4 weeks prior to screening.

7.5.3. Permitted concomitant medications

Analgesic medications which may be prescribed include acetaminophen/ paracetamol and/or propoxyphene, codeine, oxycodone, hydrocodone, and tramadol. These will be recorded in

the CRF. Acetaminophen/paracetamol with codeine or codeine-analogue may be prescribed only if necessary after the participant has failed acetaminophen according to clinician discretion.

Steroids (IA/IM) are permitted for flare in accordance with the protocol and will be recorded on the CRF. NSAIDs are permitted and will be recorded..

N.B. *All patients will receive folic acid prophylaxis e.g. generic 5mg tablets 6 days/week given orally (except day of methotrexate) as per standard of care. Folic acid will be supplied by the local NHS pharmacy. Please see section 7.1, 7.2, 7.3 for further information regarding the prescribing and administration of NIMPs.*

7.5.4. Prohibited concomitant medications

Oral corticosteroids at entry into the study

7.5.5. Surgical procedures

Are permitted if necessary, at the discretion of the physician, if there is not a break of >4 weeks in the medication. If there is a break of >4 weeks in medication then patients will have to be withdrawn.

Treatment should be omitted or continued as per the local protocol and at the discretion of the Principal Investigator.

7.6. Special warnings and precaution for use

Please refer to SPC (attached)

7.7. Dose modifications.

Up-titration of MTX will occur in accordance with standard NHS care for all groups. Similarly, other conventional DMARDs (as defined by section 1.2.2.1) may be started to replace MTX in the case of intolerance or included as an adjunct as per T2T care. These alternative DMARDs will be escalated in accordance with standard NHS care.

7.8. Assessing subject compliance with study treatment(s)

Every attempt will be made to select patients who have the ability to understand and comply with study instructions. The investigator is responsible for discussing methods to ensure high treatment compliance with the patient before randomization.

Patient compliance with the investigational product will be assessed at each study visit by review of the Study Drug Administration Log and/or direct questioning and by patients completing a diary card to record dates of administration. Deviation(s) from the prescribed dosage regimen should be documented in the CRF.

Non-compliance (including interruptions) will be defined as less than 80% or more than 120% of the prescribed dose (as an approximation assessed in clinic). Non-compliance will constitute a protocol violation.

If a patient is non-compliant with study procedures and/or study drug administration, the investigator should assess the patient to determine the reason for non-compliance and educate and/or manage the patient as appropriate to improve compliance. SEP

7.9. Withdrawal of treatment

As per section 6.4

7.9.1. Subject Compliance with study treatment(s)

Poor compliance with study visits may result in the withdrawal of patients from the study at the discretion of the investigator, in line with the withdrawal criteria described in section 6.4.

In line with usual clinical care, cessation or alteration of treatment regimens at any time will be at the discretion of attending clinicians or the participants themselves.

All participants withdrawn from the study will still attend for follow-up assessments and questionnaires and CRFs will continue to be completed.

8. METHODS OF ASSESSMENT

8.1. Assessment of primary efficacy variable:

Disease Activity Score (DAS28) Erythrocyte Sedimentation Rate method

- The Disease Activity Score (DAS28) is a combined index that measures disease activity in patients with Rheumatoid Arthritis (RA). It has been extensively validated for its use in clinical trials. It incorporates the tender 28-joint count (TJC28), the swollen 28-joint count (SJC28), erythrocyte sedimentation rate (ESR; mm/hour) and patient global/general health assessment VAS (mm)
- The DAS28 will automatically be calculated within the MACRO eCRF during the course of the study, and this may be used to inform decisions regarding treatment; the value calculated will also be computed at the analysis stage from the stored DAS28

components [18, 19]. DAS28 remission (primary endpoint) will be deemed to have been achieved if DAS28 ≤2.6.

- Tender joint count: The number of tender and painful joints will be determined by examination of 28 joints. Joints will be assessed for tenderness by pressure and joint manipulation on physical examination. The patient will be asked for pain sensations on these manipulations and watched for spontaneous pain reactions. Any positive response on pressure, movement, or both will then be translated into a single tender versus non-tender dichotomy. Joint assessments will be performed by an independent assessor to minimize bias. The same assessor should preferably perform the TJC and SJC for a given patient at each visit to minimize inter-observer variation. The independent joint assessor (IJA) will not be involved in patient care and will be instructed not to discuss disease activity or treatment with patients or the Principal Investigator.

- Swollen joint count: The number of swollen joints will be determined by examination of 28 joints. Joints will be classified as either swollen or not swollen. Swelling is defined as palpable fluctuating synovitis of the joint. Swelling secondary to osteoarthritis will be assessed as not swollen, unless there is unmistakable fluctuation. Joint assessments will be performed by an independent assessor to minimize bias. Where possible, the same assessor should preferably perform the TJC and SJC for a given patient particularly during the study to minimize inter-observer variation. The independent joint assessor (IJA) will not be involved in patient care and will be instructed not to discuss disease activity or treatment with patients or Principal Investigator.

8.2. Assessment of secondary efficacy variable(s)

Imaging

- Ultrasound assessment of power doppler synovitis (PD), grey scale (GS) changes, erosions (E) and osteophytes and tenosynovitis will be performed at baseline and 24 weeks, as per our standardised protocol:
    - Standard set of 26 joints:
        - Bilateral wrists
        - Metacarpal joints (MCP) 2 & 3
        - Proximal inter-phalangeal joints (2 & 3)
        - Elbows
        - Knees

- Ankles
- Bilateral metatarsal joints (MTP) 1-5

- Both PD and GS will be scored between 0-3. The scores for individual joints and the totals will be calculated.
- Flexor tendons 2 and 3 bilaterally (MCP and PIP level) and ECU tendons will also be scanned. Both PD and GS will be scored between 0-3 for tenosynovitis.
- Scoring:
  - PD0 = no synovitis
  - PD1 = mild synovitis, ≤3 isolated single areas
  - PD2 = moderate synovitis, >3 isolated singles or confluent signal in less than half of the synovial area
  - PD3 = marked synovitis, signals in more than half of the synovial area
  - GS0 = no grey scale (no synovial hypertrophy)
  - GS1= mild hypoechoic synovial thickening
  - GS2= moderate hypoechoic synovial thickening
  - GS3= marked hypoechoic synovial thickening

- Scans will be performed by the same dedicated ultrasonographer as per other clinical trials within the department.

- It is expected that the scans will take 45 minutes approximately.

  Prior to ultrasound, patients will be asked to stop taking any anti-inflammatory drugs (NSAIDs) e.g. ibuprofen for a minimum of 48 hours to maximise the ability for imaging to detect any inflammatory changes present. They will be able to take paracetamol and codeine-based analgesia as an alternative.

Immunological parameters

- A blood sample for T-cell subsets will be taken alongside routine blood tests. These will be processed by the NHS laboratory as it is a standard NHS test in our clinics in Leeds Teaching Hospitals.
- Naïve $CD4^+$ T-cells will be measured via cell surface antigen detection by 8-colour flow cytometry. The $CD4^+$ T-cells will first be identified by staining for the CD and CD4 markers. Naïve cells will be identified based on the high expression of CD45RB and positivity for CD45RA and CD62L. Also included in this panel will be T-regulatory cells

(Treg) and inflammation related cells (IRC's), which may be used at a later data for an exploratory immunological analysis.

- Patients' naïve T-cell frequency (%) will be compared to the level expected for their age according to the following formula derived from 106 healthy controls: (-0.54*age) + 63.19 (Please see Appendix 1). A patient whose naïve T-cell level is at or above this value will be considered to have a normal T-cell result; a patient with levels below the age-expected value will be considered to have an abnormal result[20]. Patients will not be made aware of their T-cell status, however they will be informed in the patient information sheet that patients will be randomised based on abnormal T-cells. Therefore, those receiving SB4 will know that they have abnormal T-cells. This however is acceptable as blinding is more important for the groups receiving monotherapy.

Visual Analogue Scales (VAS)

- The response to each VAS is to be marked by placing a vertical line at the point along the 100mm VAS which corresponds to the patient's condition on the day of assessment.
- **Physician Global Assessment of general health:** The investigator's evaluation of rheumatoid disease activity should be completed before the patient's global assessment of general health is received. The investigator will assess the patient's rheumatoid condition taking into account not only impressions from the assessments made in the study, but also any other information available. The investigator is required to answer the question 'What is your assessment of the patient's current disease activity'? The left end of the 100mm line corresponds to 'none' and the right end to 'extremely active'.
- **Patient Assessment of General State of Health:** The patient is required to answer the question 'How do you rate your general state of health today?' The left end of the 100mm line corresponds to 'very well' and the right end to 'very poor'. This VAS is to be completed by the patient.
- **Patient Assessment of Disease Activity:** The patient is required to answer the question 'Considering all of the ways your arthritis has affected you, how to you feel your arthritis is today'? The left end of the 100mm line corresponds to 'very well' and the right end to 'very poor'. This VAS is to be completed by the patient.
- **Patient Assessment of Pain:** The patient is required to answer the question 'What level of pain are you currently experiencing?'. The left end of the 100mm line corresponds to no pain and the right end to 'worst possible pain'. This VAS is to be completed by the patient.

Health Assessment Questionnaire (HAQ)

The Stanford Health Assessment Questionnaire was originally developed in the US[21]; although originally developed for use in patients with rheumatoid arthritis the HAQ is now considered a generic rather than disease-specific tool and has been validated for use in many disease areas[22]. The full HAQ assesses 5 dimensions of health outcome; here we use HAQ as an abbreviation of the Health Assessment Questionnaire Disability Index (HAQ-DI), which assesses a patient's level of functional ability.

There are 20 questions in 8 categories of functioning that represent different activities - dressing, rising, eating, walking, hygiene, reach, grip and usual activities. For each item there is a 4-level difficulty scale scored from 0-3, representing no difficulty (0), some (1) or much (2) difficulty, and unable to do (3). The highest component score in each category determines the category score, unless the patient uses aids or devices for, or receives assistance with activities in that category, in which case the relevant category score is increased to 2 if the maximum score was previously <2. The 8 category scores are averaged into an overall score from zero to 3, zero indicating no disability, 3 indicating complete disability. The UK version follows the same format bar some minor changes to item wording[23]. The HAQ has been shown to have good face, content and construct validity, predictive validity and is sensitive to change[22].

CDAI & SDAI:

The CDAI or Clinical Disease Activity Index [24] and the SDAI [25] or Simplified Disease Activity Index [2] are inspired by the « DAS » score family for Rheumatoid Arthritis, comprising namely DAS28 and DAS28-CRP. They are very useful to make an objective, reproducible and comparable assessment of the rheumatoid arthritis activity.

Simplified Disease Activity Index (SDAI) is a simple disease activity index for RA; composed of the numerical sum of five outcome parameters: TJC and SJC (28 joints), patient and physician's global assessment of disease activity and level of CRP (mg/L). Classic disease activity cut-offs define low disease activity as an SDAI ≤11 and remission as a SDAI ≤5. Scores range between 0-100.

The Clinical Disease Activity Index (CDAI) is derived from SDAI, but does not include measurement of acute phase response and can therefore be used to conduct a quick evaluation of disease activity at any time.

The computation of the score is done through the following equation:

$$CDAI=TJC28+SJC28+PGA+PhGA$$

The interpretation of this score ranging from 0 to 76 does not depend on its evolution over time. Generally, remission is considered achieved if the score is between 0 and 2.8 included. Low activity corresponds to >2.8 to 10 included. Moderate activity is between >10 and 22 included, while high activity is strictly above 22.

Both for CDAI and SDAI, the 28 tender or swollen joint scores target the same joints (shoulders, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints and the knees).

8.3. Assessment of other efficacy variables:

- ***Assessment of early morning stiffness (EMS):*** Duration of morning stiffness reported by subjects as the average daily length during the past week in minutes (from time of waking to time of maximal improvement, up to a maximum of 720 minutes)**.**
- ***Quality of Life Assessments/Patient-reported outcome measures***
    - Visual Analogue Scales (VAS) – as per above
    - Health Assessment Questionnaire (HAQ) – as per above

8.4. Assessment of exploratory biomarkers

- Serum and plasma samples collected will also be stored (at baseline and at Week 24 for (but not limited to) future evaluation of disease categorisation, auto-antibodies, inflammatory, immunological and vascular biomarkers and products of synovial, cartilage and bone turnover in this and future studies (subject to ethical review of such studies).

9. STUDY PROCEDURES BY VISIT

Note: All timed visits post-screening should take place within a seven-day window of the scheduled visit time.

All study visits falling outside this window will be reported to the Sponsor QA Office on the designated protocol deviation form, in-line with the corresponding Sponsor SOP.

9.1 Summary schedule of study assessments

Timepoint	**Wk -4 to 0**	**Wk 0**	**Wk 4***	**Wk 12***	**Wk 24***	**Unscheduled Visit**
Study phase	**Screening**	**Baseline**	**Safety**	**Secondary outcomes**	**Primary outcome**	**-**
Visit	*1*	*2*	*3*	*4*	*5*	*6*
Inclusion/Exclusion Criteria	x	x				
Informed Consent[1]	x	x	x	x	x	x
Randomisation		x				
Adverse event assessment			x	x	x	x
Patient demographic data	x					
Vital signs/observations (height, weight, BP, heart rate, temperature)	x					
Medical/surgical/family history	x					
Concomitant medications	x	x	x	x	x	x
Clinical assessment data (TJC & SJC [via IJA], DAS28, EMS)	x	x	x	x	x	x[a]
General Physical Examination [2]	x					
Patient reported outcome questionnaires (VAS pain, disease activity & general health, HAQ-DI)	x	x	x	x	x	x[a]
Autoantibodies (RF, ACPA, ANA) [3]	x					
Naïve $CD4^+$ T-cells[3]	x			x	x	x[a]
Inflammatory markers (ESR & CRP)	x	x	x	x	x	x[a]
Stored blood sample for exploratory biomarkers		x			x	
Haematology (FBC)	x	x	x	X	x	x[a]
Biochemistry (eGFR, LFT, U&E)	x	x	x	X	x	x[a]

Timepoint	**Wk -4 to 0**	**Wk 0**	**Wk 4***	**Wk 12***	**Wk 24***	**Unscheduled Visit**
Study phase	**Screening**	**Baseline**	**Safety**	**Secondary outcomes**	**Primary outcome**	**-**
Visit	*1*	*2*	*3*	*4*	*5*	*6*
MSK Ultrasound 26 joints and 6 tendons+		x			x	x[a]
Physician assessment of general health (VAS)	x	x	x	x	x	x[a]
Chest X-Ray[4]	x					
TB (QuantiFERON)[5]	x					
Hepatitis B (HB Antigen, HB core antibody)[5]	x					
Hepatitis C[5]	x					
HIV Screen[5]	x					
Urinalysis [Dipstick] [6]	x					
Pregnancy test[6]	x					
IMP initial administration time point+		x				
Document steroid use, method of administration and dose		x	x	x	x	x
Adverse event recording			x	x	x	x
Compliance assessment (IMP)			x	x	x	x

1. Written consent at screening & checking of consent at subsequent visits

2. Full systems examination to include cardiovascular, respiratory and abdominal examination. This is mandatory at screening visit and may be performed if clinically indicated (system-dependent) at other visits.

3. If not done within 4 weeks (may have been routinely assessed in EAC)

4. If subjects have a chest x-ray performed within the last 24 weeks, a new chest x-ray will not be performed in order to minimize exposure to x-ray radiation.

5. If not already performed within the last 12 weeks (may have been routinely assessed in EAC)

6. Urinalysis and Pregnancy test can be repeated at other visits if clinically indicated.

a. These assessments will only be carried out if the reason for the "unscheduled visit" is a flare.

* The permitted window for these study visits is +/- 7 days.

+ Research activity to occur +/- 7 days from clinic visits.

9.2 Screening visit (Weeks -4 to 0)

The screening period should not last longer than four weeks. The aim of the screening visit is to identify a patient who might be suitable for inclusion in the study. The following will be performed at this visit (and recorded in the CRF):

- ***General***
    - Obtain written consent: The patient will have received information, including the Patient Information leaflet, at least 24 hours before the screening visit. Their knowledge of the nature and objectives of the study will be verified and his/her informed consent will be obtained.
    - Subject number assigned
    - Check patient eligibility
    - Patient demographic data:
        - Age (years)
        - Sex
        - Ethnic group
    - Clinical observations:
        - Height (cm)
        - Weight (kg)
        - BMI calculation (kg/m$^{2)}$
        - Blood pressure (mmHg) & heart rate (bpm)
        - Temperature
    - Concomitant medications/allergy history
    - Detailed surgical/medical/social history
    - Detailed family history (autoimmune, vascular & rheumatic disease)
    - Smoking history
    - Alcohol intake (units/week)

- ***Laboratory Tests***
    - Routine haematology and biochemistry suitable for diagnostic investigation: FBC, U&E, LFT & eGFR ml/min/1.73 m^2
    - ESR (mm/h) & CRP (mg/L)
    - Rheumatoid factor (RF) titre+
    - Anti-nuclear antibody (ANA) titre+
    - Anti-citrullinated protein antibody (ACPA) titre+

- Naïve $CD4^+$ T-cell measurement+
- Hepatitis B&C screen (Hep B surface antigen, Hep B core antibody, anti-HCV antibody)*
- HIV Screen*
- QuantiFERON test for TB*
- Urinalysis for blood, protein and nitrites to exclude infection/renal disease
- Pregnancy test for women with childbearing potential

**If not already performed within the last 12 weeks (may have been routinely assessed in EAC)*

+ If not already performed within last 4 weeks (may have been routinely assessed in EAC)

- ***Clinical assessment data***
  - Joint examination performed by an independent assessor:
    - Tender joint count (28)
    - Swollen joint count (28)
  - Disease activity score (DAS28)
  - Clinical disease activity Index (CDAI)
  - Simplified disease activity index (SDAI)
  - Early morning stiffness (mins)
  - Full physical examination (including cardio-respiratory and abdominal systems)

- ***Patient reported outcomes***
  - Visual analogue scores of pain/disease activity/general health
  - Physician assessment of general health
  - HAQ-DI

    Note*: Whenever possible, physician VAS assessments should be performed by the same investigator*

- ***Imaging***
  - Chest X-Ray (if not been done within the last 24 weeks)

- ***Randomisation***
    - Randomisation to treatment arms (for patients with abnormal T-cell status) can only happen once the investigation in possession of the T-cell report.

      N.B. this must take place <u>prior</u> to the patient attending the baseline visit

*9.3 Baseline visit & IMP commencement (Week 0)**

* Visit to occur within 4 weeks after screening visit

- ***General***
    - Confirm eligibility by review of inclusion/exclusion criteria and consent
    - Clinical observations will be performed as per standard care (not required as a research parameter)
    - Medication, allergy and co-morbidity check

- ***Clinical assessment data***
    - Joint examination performed by an independent assessor:
        - Tender joint count (28)
        - Swollen joint count (28)
    - Disease activity score (DAS28)
    - Clinical disease activity index (CDAI)
    - Simplified disease activity index (SDAI)
    - Early morning stiffness (mins)
    - Cardio-respiratory & abdominal examinations if clinically indicated

- ***Patient reported outcomes***
    - Visual analogue scores of pain/disease activity/general health
    - Physician assessment of general health
    - HAQ-DI
- ***Laboratory tests***
    - Routine haematology and biochemistry suitable for diagnostic investigation: FBC, U&E, LFT & eGFR ml/min/1.73 m^2

- ESR (mm/h) & CRP (mg/L)
- Biologic blood sample collection for storage (exploratory biomarkers)
- Urinalysis/pregnancy test if clinically indicated

- ***Imaging***
  - Power Doppler Ultrasound (PDUS) of standard set of 26 joints and 6 tendons for grey-scale (GS), power Doppler (PD), erosions (E) and osteophytes (O) and tenosynovitis (TSV) (+/- 7 days from clinic visit)
    - To be performed prior to first administration of study treatments
- ***Adverse event recording***
- ***Initiation of DMARD treatment as per T2T*** (up to 7 days from clinic visit).
- ***Initiation of Benepali® for ARM C*** (up to 7 days from clinic visit).
  - Patients taught how to self-inject
- ***Offer IM/IA/PO corticosteroids as appropriate (in line with standard practice)***
- ***Document steroid used, dose and method of administration***

9.4 Follow up visits

9.4.1 Week 4 (Safety visit) (+/- 7 days)

As per standard clinical care/T2T, patients will undergo the following routine clinical & laboratory assessments:

- ***General***
  - Confirm eligibility and consent
  - Assess compliance with treatment
  - Clinical observations will be performed as per standard care (not required as a research parameter)
  - Medication, allergy and co-morbidity check
- ***Clinical assessment data***
  - Joint examination performed by an independent assessor:

        - Tender joint count (28)
        - Swollen joint count (28)
    - Disease activity score (DAS28)
    - Clinical disease activity index (CDAI)
    - Simplified disease activity index (SDAI)
    - Early morning stiffness (mins)
    - Cardio-respiratory & abdominal examinations if clinically indicated

- ***Patient reported outcomes***
    - Visual analogue scores of pain/disease activity/general health
    - Physician assessment of general health
    - HAQ-DI

- ***Laboratory Tests***
    - Routine haematology and biochemistry suitable for diagnostic investigation & therapeutic DMARD monitoring FBC, U&E, LFT & eGFR ml/min/1.73 m^2
    - ESR (mm/h) & CRP (mg/L)
    - Urinalysis/pregnancy test if clinically indicated

- ***Other:***
    - Adverse event recording
    - DMARD management according to T2T and the physician's discretion. +/- IM/IA/PO corticosteroids as appropriate (in line with standard practice)
    - Document steroid used, dose and method of administration

9.4.2. Week 12 (Secondary Outcomes) (+/- 7 days)

As per standard clinical care/T2T, patients will undergo the following routine clinical & laboratory assessments:

- ***General***
    - Confirm eligibility and consent
    - Assess compliance with treatment
    - Clinical observations will be performed as per standard care (not required as a research parameter)
    - Medication, allergy and co-morbidity check

- ***Clinical assessment data***
    - Joint examination performed by an independent assessor:
        - Tender joint count (28)
        - Swollen joint count (28)
    - Disease activity score (DAS28)
    - Clinical disease activity index (CDAI)
    - Simplified disease activity index (SDAI)
    - Early morning stiffness (mins)
    - Cardio-respiratory examination if clinically indicated

- ***Patient reported outcomes***
    - Visual analogue scores of pain/disease activity/general health
    - Physician assessment of general health
    - HAQ-DI
- ***Laboratory tests***
    - Routine haematology and biochemistry suitable for diagnostic investigation & therapeutic DMARD monitoring FBC, U&E, LFT & eGFR ml/min/1.73 m^2
    - ESR (mm/h) & CRP (mg/L)
    - Urinalysis/pregnancy test if clinically indicated
- ***Adverse event recording***

- ***DMARD management according to T2T pathway. (Assessment of remission target will be done after 12 weeks of treatment) +/- IM/IA/PO corticosteroids as appropriate (in line with standard practice) .***
- ***Document steroid used, dose and method of administration***

9.4.3. Week 24 (Primary Outcome) (+/- 7 days)

- As per week 12 plus:
    - ***Imaging*** (+/- 7 days from clinic visit)***::*** Power Doppler Ultrasound (PDUS) of standard set of 26 joints and 6 tendons for grey-scale (GS), power Doppler (PD), erosions (E) and osteophytes (O) and tenosynovitis (TSV)
    - Biologic blood sample collection for storage (exploratory biomarkers)
- In line with usual clinical care/T2T, cessation or alteration of treatment regimens at any time will be at the discretion of attending clinicians or the participants themselves.
- All participants withdrawn from treatment(s) will still attend for follow-up assessments and questionnaires and CRFs will continue to be completed.

9.4.4. Early withdrawal visit

- Not applicable as will continue to be followed up as per standard NHS/T2T care

9.4.5. Safety follow-up visit

- Not applicable as will continue to be followed up as per standard NHS/T2T care

9.4.6. Unscheduled visits

- For patients who do not tolerate their medication or are flaring outside of the study schedule.
- Will be recorded in the medical notes and in the CRF.
- If side effects related to IMP to be recorded as an adverse event
- Any changes to treatment to be documented

- ***General***
    - Assess compliance with treatment
    - Clinical observations will be performed as per standard care (not required as a research parameter)
    - Medication, allergy and co-morbidity check
- ***Clinical assessment data***
    - Physical examination if clinically indicated
- ***Laboratory tests***
    - Routine haematology and biochemistry suitable for diagnostic investigation & therapeutic DMARD monitoring FBC, U&E, LFT & eGFR ml/min/1.73 m^2
    - Urinalysis/pregnancy test if clinically indicated
- ***Adverse event recording***

If the reason for the visit is a flare, the following assessments will also be done:

- ***Clinical assessment data***
    - Joint examination performed by an independent assessor:
        - Tender joint count (28)
        - Swollen joint count (28)
    - Disease activity score (DAS28)
    - Clinical disease activity index (CDAI)
    - Simplified disease activity index (SDAI)
    - Early morning stiffness (mins)
- ***Laboratory tests***
    - *Naïve CD4+ T-cells*
    - ESR (mm/h) & CRP (mg/L)
- ***Patient reported outcomes***
    - Visual analogue scores of pain/disease activity/general health
    - Physician assessment of general health
    - HAQ-DI

- ***Imaging***
    - Power Doppler Ultrasound (PDUS) of standard set of 26 and 6 tendons joints for grey-scale (GS), power Doppler (PD), erosions (E) and osteophytes (O) and tenosynovitis (TSV)
- Management of DMARD treatment/administration of corticosteroid treatment will be at the discretion of the treating study physician

10. PHARMACOVIGILANCE

10.1 Defining adverse events

An **adverse event** (AE) is any untoward medical occurrence in a patient during or following administration of an investigational product and which does not necessarily have a causal relationship with treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of the trial drugs, whether or not considered related to the trial drugs.

10.2 Defining serious adverse events (SAEs)

A **serious adverse event** (SAE) is an adverse event which is defined as serious, i.e. that it:

- Results in death. Death may occur as a result of the basic disease process. Nevertheless, all deaths occurring within 30 days of the last administration of the study agent must be treated as an SAE and reported as such. All deaths which may be considered as related to the trial agent, regardless of the interval, must be treated as a SAE and reported as such.
- Is life-threatening.
- Requires inpatient (overnight) hospitalization or prolongation of an existing hospitalization.
- Results in a persistent or significant disability or incapacity.
- Results in a congenital anomaly or birth defect.
- Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- Any other significant clinical event, not falling into any of the criteria above, but which in the opinion of the Investigator requires reporting.

Other Reportable Information: Certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes the following:

- Pregnancy exposure to an IMP except for exposure to prenatal vitamins.
- Lactation exposure to an IMP, with or without an AE.
- Overdose of an IMP as specified in this protocol, with or without an AE. Baby formula overdoses without any AEs are excluded.
- Inadvertent or accidental exposure to an IMP, with or without an AE.
- Routine planned surgery

10.3. AEs of special interest

10.3.1. Pregnancy

Pregnancy is considered a form of SAE. If a pregnancy is confirmed, use of the IMP must be discontinued immediately. Both maternal and paternal exposures are considered other reportable information. For exposure involving the female partner of a male subject, the necessary information must be collected from the subject, while respecting the confidentiality of the partner. All pregnancies will be followed up until birth.

10.4. Exemptions from safety reporting

10.4.1. Efficacy endpoints and disease progression events

All events that are unequivocally due to progression of moderate to severe rheumatoid arthritis or lack of response should not be reported as an AE or SAE. This type of information will be captured in the study assessments.

Disease progression would include: increased joint pain, musculoskeletal pain, generalized body aches, uncontrolled RA, joint swelling, increased stiffness, limited motion, synoviorthesis (in or out of the hospital), and hospitalizations for RA-related procedures (joint replacement surgery, joint arthroscopy, synovectomy).

10.4.2. Defining suspected unexpected serious adverse reactions (SUSARs)

A **Suspected Unexpected Serious Adverse Reaction** (SUSAR) is a serious adverse event suspected to have a reasonable causal relationship to the investigational medicinal product where the nature or severity of the reaction is inconsistent with the available Reference

Safety Information, referring specifically to Section 4.8 'Undesirable effects' within the Summary Product Characteristics (SPC) for Benepali.

All SAEs assigned by the CI (or delegated clinician) as both suspected to be related to the trial drugs and unexpected are subject to expedited reporting.

10.5. Recording and reporting of AEs

10.5.1. Recording and reporting of all AEs

Determination of AEs should be based on the signs or symptoms detected during the physical examination and on clinical evaluation of the subject, and should be assessed and recorded at every visit. Signs and symptoms must be recorded using standard medical terminology. Subjects considered incapable of giving consent would not be considered for this study.

AEs and SAEs will be collected from the signing of the informed consent form until the last follow up visit. The Investigator must instruct the subject to report AEs and SAEs during this time period.

During the time period specified above, the Investigator will:

- Record all AEs and SAEs on source documents.
- Record all AEs and SAEs in the CRF for subjects who are not screen failures.

The Investigator must follow up on all AEs and SAEs until the events have subsided, returned to baseline, or, in case of permanent impairment, until the condition has stabilized, within the duration of the trial for each participant. There will be no follow up of AE's past the last follow up visit for each participant.

10.6. SAE and SUSAR reporting requirements

All SAEs assigned by the local Principal Investigator as both suspected to be related to protocol-treatment and unexpected will be reviewed by the Chief Investigator (CI). The CI, local PI or other medically qualified and delegated individual may declare an SAE a SUSAR.

All investigators should refer to the trial-specific Reference Safety Information when determining whether a SAE is expected [specifically Section 4.8 'Undesirable effects' within the Summary Product Characteristics (SPC) for Benepali.

All SAEs, other information reportable as SAEs and follow-up information must be reported to the Sponsor QA office within 24 hours of the research team becoming aware of them, by emailing a completed SAE form 'CTT21 Serious Adverse Event Report' to the email address (leedsth-tr.sponsorqa@nhs.net). The Sponsor will confirm that the email was received.

In parallel, the research team must also notify the study funder (Samsung Bioepis) within one business day from first awareness of the event.

Suspected adverse reactions that are both serious and unexpected are subject to expedited reporting to the REC and MHRA.

Identifiable patient data, other than linked anonymised data required by the SAE form, must not be included when reporting SAEs and SUSARs.

The Sponsor[1] then will inform the MHRA[2,3] [via the MHRA eSUSAR web portal] and the Research Ethics Committee[2,3] (REC) of SUSARs within the required expedited reporting timescales.

1. All SUSARs must be reported to the QA Sponsor office via (leedsth-tr.sponsorqa@nhs.net) within 24 hours of the event being reported to the CI (or their research team).
2. SUSARs must be reported to the REC / MHRA within 7 calendar days of the CI (or their research team) being informed of the event, if they result in Death or are deemed to be life-threatening. Follow-up information must be reported within 8 calendar days.
3. Any SUSARs not resulting in death or deemed to be life-threatening must be reported to the REC / MHRA within 15 Calendar days of the CI (or their research team) being informed of the event. Follow-up information must be reported within 8 calendar days.

   SUSARs will be reported in accordance with the requirements and provisions of the applicable national laws. They will all be signed off by the Chief Investigator or, in their absence, by a delegated individual.

10.6.1. Urgent safety measures

If the research team becomes aware of information affecting the risk/benefit balance of the trial they may take immediate action to ensure patient safety. Urgent safety measures deemed necessary must be reported immediately by telephone to the MHRA (in conjunction with the Sponsor) and to the main REC for the trial, and must be followed within three days by notice in writing setting out the reasons for the urgent safety measures and the plan for further action. The REC co-ordinator will acknowledge within 30 days.

10.6.2. Serious breaches of protocol

A **serious breach** is a breach which is likely to effect to a significant degree either:

- The safety or physical or mental integrity of the subjects of the trial; or the scientific value of the trial.

Serious breaches of GCP, the trial protocol and the Clinical Trial Authorisation will be reported to the Sponsor QA office within 24 hours from the time the research team becomes aware of the incident.

10.6.3. Laboratory measurements

The laboratory measurements to be collected in this study include haematology, clinical chemistry, pregnancy testing (for females of childbearing potential), urinalysis, CRP, ESR and immunological measurements (T-cell subsets). The blood will be drawn and sent to the laboratory in accordance with standard NHS practice.

T-cell samples will be sent for flow-cytometry. Sample labels containing appropriate identification information will be provided.

In addition to the above, a maximum of 40ml of blood will be drawn and stored for exploratory soluble biomarker testing at baseline and week 24. Approximately an additional 25 ml will be collected at visits 2-5.

10.6.4. Annual reports

Annual Safety Report

An annual report describing any relevant safety data related to the trial must be submitted to the main REC, MHRA and the Sponsor within 60 days of the anniversary of the Clinical Trial Authorisation being granted.

This annual safety report should follow the format of a Developmental Safety Update Report (DSUR). A template and guidance for the completion of this report is available from the Sponsor QA Office.

Annual Progress Report

A progress report must be submitted annually to the REC which gave the favourable opinion, following the anniversary on which the favourable opinion was first given.

A copy signed by the CI must be emailed to the REC and Sponsor within 30 days of the end of the reporting period.

10.6.5. End of trial notification and report

Upon completing the trial, as defined in section 6.5.7, an end of trial declaration must be submitted to the MHRA within 90 days of the end of the trial (or 15 days if premature termination) by the Sponsor or Sponsor-delegated individual.

All trial activities (i.e. follow-ups, visits) should be completed before the submission of the end of trial declaration form.

Within one year of the end of trial for non-paediatric clinical trials, the sponsor (or their delegated) will be responsible for uploading the end of trial summary report to EudraCT as per the commission's guidelines on posting and publication of result-related information.

A copy of this end of trial report should also be supplied to all support departments involved in the study, for example pharmacy and or radiology. The CI must review and sign / date the report.

11. STUDY MANAGEMENT AND ADMINISTRATION

11.1. Good clinical practice (GCP) and regulatory compliance

This clinical trial, which involves the use of an investigational medicinal product has been designed and will be run in accordance with the Principles of GCP and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004 / 1031) and any subsequent amendments of the clinical trial regulations.

11.2. Adherence to protocol

The Investigator should not deviate from the protocol. In medical emergencies, the Investigator may use his/her medical judgment and may remove a study participant from immediate hazard before notifying the Sponsor, the MHRA and the REC in writing regarding the type of emergency and the course of action taken.

11.3. Monitoring, audit and inspection

The Sponsor reserves the right to audit any site involved in the trial and authorisation for this is given via the study contract or agreement. A site may be audited, by LIRMM, an independent contractor working for LIRMM or may be subject to inspection by the MHRA at any time in order to ensure compliance with ICH-GCP, and the Investigator should allow direct access to trial documentation.

11.3.1. Procedures for monitoring subject compliance

Patients will be asked regarding compliance with treatment at each study visit; diary cards will also be used to support the review of patient IMP compliance.

Members of the research team will review compliance at each clinic visit before returning the diary to the patient. This compliance review will be detailed in the medical notes.

11.3.2. Definition of source data

Source documents are original records in which raw data are first recorded. These may include, e.g. hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, or other printouts, completed scales, or Quality of Life Questionnaires. Source documents will be kept in a secure, limited access area.

Some data will be recorded directly in the CRF and will not appear in a physical source document [as defined in the Source Data Location Sheet document].

Source documents that are computer-generated and stored electronically will wherever possible be printed and filed in the patient medical notes for review by the monitor/inspector.

The Investigator will authorize the monitor to compare the content of the print out and the data stored in the computer to ensure all data are consistent. If electronically stored and impractical to print, each timely review of the electronically stored data will be annotated in the patient's notes.

Electronic data records such as x-ray and ultrasound records will be saved and stored in an appropriately secure location as described in the Source Data Verification form

11.3.3. Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (e.g. subject files, recordings from automated instruments, x-ray films and laboratory notes). All data reported on the CRF should be supported by source documents, unless otherwise specified in section 11.3.2. Data Verification and will be carried out by the investigators and members of the study team who will check the case report forms for completeness and clarity, and crosscheck them with source documents.

11.3.4. Quality assurance

Investigators will promptly notify the Sponsor Quality Assurance Office of the following within the required timeframe:

- Serious breaches of GCP
- Urgent safety measures
- Protocol violations
- Any amendments to the trial
- Any changes the Clinical Trial Risk Assessment (form A).
- Any other issues as stated in the study contract or agreement

11.3.5. Trial oversight

The trial will be overseen at all times by the Sponsor, The University of Leeds. It is expected that the joint Sponsor office will monitor and audit the study on in accordance with the trial-specific monitoring plan (TMP). A copy of the TMP can be found filed in the Trial Master File. The local study team will have day-to-day oversight, led by the PI.

The research team will also utilise the in-house Clinical Trials Associate to routinely monitor the study (also see TMP). The study will also be discussed at regular trial update meetings to review any issues or potential concerns. The trial research team can then feed back to the trial steering committee where required.

11.3.6. Trial steering committee (TSC)

Independent oversight of the study will be conducted by the Trial Steering Committee. Amongst its members will be an independent chair (clinician), a clinician who is independent of the study research team, and a representative of the LIRMM study management team. Additional members may be appointed at the discretion of the CI. They are expected to meet at least six-monthly.

Trial Steering Committee Terms of Reference:

Specifically, the Trial Steering Committee will be responsible for monitoring the following:

I. Patient Safety

II. Adherence to Protocol

III. To monitor and supervise the progress of the trial towards its interim and overall objectives.

IV. To review and consider, at regular intervals, new and relevant information from other sources (e.g. other related trials).

V. In light of any significant issues, concerning any of the above, to inform the Sponsor on the progress of the trial.

11.4. Data handling

11.4.1. Electronic CRF completion

The research team is responsible for prompt reporting of accurate, complete, and legible data in the eCRF and in all required reports.

Any change or correction to the electronic CRF will be time-stamped and documented within the data storage system, with all previous versions of the form being retained for future reference.

The Investigator will maintain a list of personnel authorized to enter data into the CRF.

11.4.2. Database entry and reconciliation

Source data will be transcribed into the eCRF, which also incorporates a validated electronic database, using a research data management system (MACRO). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. Data will be entered into the research database using a rolling query-resolution system designed to identify data entry errors and protocol deviations in a timely fashion to allow accurate reconciliation.

An electronic audit trail system will be maintained within the MACRO system to track all data changes in the database once the data has been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

11.4.3. Screening and enrolment logs

Subject's Screening will be recorded in the Subject Screening Log.

The Investigator will keep a list containing all subjects enrolled into the study. This list remains with the Investigator and is used for unambiguous identification of each subject. The list contains the subject identification number, full name, date informed consent signed, date of screening, and the hospital number or National Health Security number, if applicable.

The subject's consent and enrolment in the study must be recorded in the subject's medical record. These data should identify the study and document the dates of the subject's participation.

11.5. Archiving and data retention

In line with the principles of GCP / UK Clinical Trial Regulations, at the end of the trial, essential documents will be securely archived at each participating centre for a minimum of 25 years. However, because of international regulatory requirements, the Sponsor may request retention for a longer period. Arrangements for confidential destruction will then be made. If a patient withdraws consent for their data to be used, it will be confidentially destroyed

immediately. No records/study documentation/data may be destroyed without first obtaining written permission from the Sponsor.

Essential documents include (this list is not exhaustive):

- Signed informed consent documents for all subjects.
- Subject identification code list*, screening log (if applicable) and enrolment log.
- Record of all communications between the Investigator, the REC and the Sponsor.
- Composition of the REC, and the Sponsor (or other applicable statement as described in section 13.6).
- List of sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant trial-related duties, together with their roles in the study and their signatures.
- Copies of case report forms and documentation of corrections for all subjects.
- Investigational product accountability records.
- Record of any body fluids or tissue samples retained.
- All other source documents (subject medical records, hospital records, laboratory records, etc.).
- All other documents as listed in section 8 of the ICH E6 Guideline for Good Clinical Practice (Essential Documents for the Conduct of a Clinical Trial).

  *European Union legislation requires this list to be maintained for a minimum of 15 years.

Normally, these records will be held in the Investigator's offsite archives.

If the Investigator is unable to meet this obligation, he or she must ask the Sponsor for permission to make alternative arrangements. Details of these arrangements should be documented.

11.6. Study suspension, termination and completion

Suspension or termination of the study may occur at any time for any reason, following discussion between the Investigator and the Sponsor. In the case of early study termination, the Sponsor or delegated individual will be responsible for completing a premature end of study report to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC) within 15 days. Upon study completion, the Sponsor or Sponsor-delegated individual will be responsible for sending the Declaration of the End of a Clinical Trial to the MHRA within 90 days. The Sponsor or Sponsor-delegated individual will be responsible for providing the end of trial report to the MHRA within 1 year of the end of the trial.

12. DATA EVALUATION

12.1. Responsibilities

The trial statistician will be responsible for producing the final data report.

12.2. Hypotheses

The primary alternative hypothesis is that the difference (Δ) in the proportions of patients in clinical remission (DAS28 ≤2.6) after 6 months of first-line treatment with MTX monotherapy between those with normal (Arm A) vs. abnormal (Arm B) naive $CD4^+$ T-cell frequencies will differ from 0.

H_0: $\Delta = 0$

H_1: $\Delta \neq 0$

12.3. General statistical considerations

Unless otherwise specified, the last valid measurement before study medication administration will be utilized as the baseline value. In general, summary statistics [n (number of available measurements), arithmetic mean, standard deviation, median, minimum, and maximum] for quantitative variables and absolute and relative frequency tables for qualitative data will be presented.

Wherever possible the trial will be reported in accordance with the recommendations of the CONSORT (Consolidated Standards of Reporting Trials) statement.

This trial includes both a confirmatory comparison (arm A vs arm B) and a pilot comparison (arm B vs arm C). For comparisons between arms A and B, two-tailed significance tests will be conducted at the 5% level of significance. Comparisons between arms B and C will be purely descriptive.

A detailed statistical analysis plan (SAP) will be completed prior to the final lock of the database; any differences between the final analysis and the SAP will be documented in the trial report.

12.4 Analysis sets

Full analysis set (FAS): The FAS will include all patients randomised. Following the intent-to-treat principle, patients will be analysed according to the treatment assigned irrespective of treatment received.

Per protocol set (PPS): The PPS will include patients in the FAS who have no significant deviations from the protocol that may influence the viability of the data.

Safety set: The Safety set will include all patients who took at least 1 dose of study treatment during the treatment period. Patients will be evaluated according to study treatment received.

12.5. Planned efficacy analyses

12.5.1. Primary endpoint analysis

The primary endpoint analysis will be conducted in the FAS. Binary logistic regression will be used to compare the proportion of patients achieving clinical remission at 6 months between arms A and B, adjusting for DAS28 at baseline. Both unadjusted and adjusted odds ratios will be presented, together with 95% confidence intervals.

12.5.2. Secondary endpoint analyses

Secondary endpoint analyses will be conducted in the FAS. The proportions of patients in clinical and imaging remission at 3 & 6 months will be compared between arms A and B in the same manner as the primary analysis (analyses of imaging remission will adjust for the number of joints scoring PD>0 at baseline).

Patient-reported outcomes at 3 and 6 months will be compared between arms A and B using non-parametric quantile (median) regression, controlling for baseline values in each case. Unadjusted and adjusted differences will be presented, together with 95% confidence intervals.

For comparisons between Arms B and C, descriptive summaries of all endpoints will be presented within each arm. Unadjusted and adjusted between-group differences and a range of 90% confidence intervals (75%, 85%, 90%, 95%) will be presented but no inferential tests will be conducted. Assuming preliminary proof of concept is obtained (i.e. the proportion of patients in clinical remission at 6 months is higher in arm C than arm B), sample size

calculations will be performed for a range of plausible and clinically meaningful between-group differences

12.5.3. Other analyses

Sensitivity analyses of the primary and secondary outcomes will be repeated in the per protocol set.

Previously published research suggested that the optimal naive CD4 T-cell frequency cut-off for prediction of response to MTX monotherapy was equivalent to the expected value for the patient's age. We will verify this by pooling the patients in arms A and B and using non-parametric ROC curve analysis, taking clinical remission at 6 months as the reference variable and age-corrected baseline naive $CD4^{\pm}$ T-cell frequency as the classification variable. Area under the ROC curve and the 95% confidence interval will be presented. The point at which the Youden Index (J = sensitivity + specificity – 1) is maximised will be chosen as the optimal cut-off. We will additionally investigate whether there is evidence that baseline DAS28 affects the accuracy of classification by including it as a covariate in a secondary ROC analysis.

12.6. Safety analyses

Safety analyses will be conducted in the safety set. Line listings of all SAEs will be provided in the end of trial report. The frequency of all SAEs during the study period will be presented for each treatment group separately. The data will be displayed as number of subjects experiencing the SAEs, percentage of subjects, and number of SAEs. Data will also be corrected for exposure by 100 patient-years.

12.7. Handling of dropouts and missing data

Wherever possible, patients who discontinue study treatment will continue to be followed up according to the study visit schedule. Patients who discontinue study treatment early due to lack of efficacy will be considered non-responders from that point onward (not achieving clinical or imaging remission). In the main analysis, patients with missing data for reasons other than lack of efficacy will also be considered non-responders; sensitivity analyses will include best-case and worst-case single imputation for these patients, complete case analysis and, if possible, multiple imputation. For patient-reported outcomes, the primary analysis will only include patients with data available; sensitivity analyses will include best-case and worst-case single imputation for patients with missing data and, if possible, multiple imputation.

12.8. Planned interim analysis and data monitoring

There are no interim analyses planned for this small, short-term study. In addition to standard monitoring by the sponsor during the trial, there will be a blind data review by the trial statistician prior to the final database lock.

12.9. Determination of sample size and randomization method

We will allocate the patients to arm A if the patient's naive $CD4^+$ T-cell frequency is normal for their age and gender. In our previous pilot study 42% of comparable RA patients had abnormal frequency values, of whom 25% responded to MTX at 6 months compared to 68% of those with normal values. Those with abnormal values will be (randomly permuted block) randomised 1:1 to arm B or C, therefore this would result in an approximate 2.75:1 ratio of patients in arms A and B. For the primary outcome of clinical remission at 24 weeks, at the 5% level of significance, to achieve 80% power to detect a difference between the target proportions of patients achieving clinical remission in arms A (68%) and B (25%)[25], a total of 53 patients would be required, assuming binary logistic regression with a variance inflation factor of 1.05 estimated from pilot data. We will increase the sample size to n=60 to account for 10% drop-out. The total number needed to be recruited to the study would therefore be 76 (44 in arm A, 16 in arm B and 16 in arm C).

To have a more robust estimate of the proportion of clinical remission in arm B and C, recruitment will continue until at least 34 and no more than 60 patients with abnormal T-cell values have been randomised 1:1 to arm B or C, and there are at least 46 patients in arm A. Thus the total sample size for the study is anticipated to be between 76 (approximately A=44, B=16, c=16) and 106 patients (approximately A=46, B=30, C=30). In the case where recruitment within Arm A is disproportionately recruiting more than Arm B or C, recruitment will stop within Arm A once minimum recruitment number has been reached. Patients will not be disadvantaged as they will still receive Treat to Target care.

12.10. Procedure for un-blinding the study prior to analysis

The trial statistician will remain blind to naive $CD4^+$ T-cell status (normal/abnormal) and treatment arm during an initial review of the data prior to the final database lock. Once the review is complete, any necessary amendments to correct data entry errors have been made, and the SAP updated to reflect any additional sensitivity analyses required, the date the statistician received the identification codes for the 3 study arms will be formally recorded in the trial documentation before the analysis can begin.

13. ETHICS AND REGULATORY REQUIREMENTS

13.1. Good Clinical Practice

This study will be conducted in accordance with applicable laws and regulations including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) and the recommendations guiding ethical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 48th General Assembly, Somerset West Republic of South Africa, October 1996. The Research Ethics Committee (REC) and MHRA must review and approve the protocol and informed consent form before any subjects are enrolled. Before any protocol-required procedures are performed, the subject must sign and date the REC-approved informed consent form. The right of a patient to refuse participation without giving reasons must be respected. The patient must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment. The study will be submitted to and approved by a main Research Ethics Committee (REC) and the appropriate regulatory authorities prior to entering patients into the study.

13.2. Delegation of Investigator duties

The Principal Investigator should ensure that all persons assisting with the trial are adequately qualified and informed about the protocol, any amendments to the protocol, the study treatments, and their trial related duties and functions.

The Principal Investigator should maintain a delegation log of co-investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties. The delegation log will be kept within the investigator site file.

13.3. Subject information and informed consent

Before being enrolled in the clinical study, subjects must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to them.

An informed consent document (Patient Information Leaflet) that includes both information about the study and the consent form will be prepared and given to the subject at least 24 hours prior to the screening visit. This document will contain all the elements required by the ICH E6 Guideline for Good Clinical Practice and any additional elements required by local regulations. The document must be translated (by an independent interpreter) into a language understandable to the subject and must specify who informed the subject. Where required by local law, the person who informs the subject must be a physician.

At the screening visit, patients will be given the opportunity to ask questions and the nature and objectives of the study will be explained. A research nurse may help in this process but the study doctor is responsible for the informed consent discussions.

After reading the informed consent document, the subject must give consent in writing. The subject's consent must be confirmed at the time of consent by the personally dated signature of the subject and by the personally dated signature of the person conducting the informed consent discussions, the study doctor.

The original signed consent document will be retained in the Study Files. Other copies of the consent form are required:

- One copy of the informed consent document will be kept in the patient's clinical notes.
- One copy will be given to the patient.

Consent is an ongoing process and will be reassessed at each study visit.

The Investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

The Investigator must inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

13.4. Subject confidentiality

Only the subject number will be recorded in the case report form, and if the subject name appears on any other document (e.g. laboratory report), it must be obliterated on the copy of the document to be supplied to anyone outside the clinical care team. The subjects will be informed that representatives of the Sponsor, Research Ethics Committee (REC) or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence.

All information collected during the course of the trial will be kept strictly confidential.

Information will be held securely on paper and also electronically.

The Leeds Institute for Rheumatology and Musculoskeletal Medicine/Leeds Musculoskeletal Biomedical Research Unit will comply with all aspects of the Data Protection Act 2018.

The Principle Investigator at each site will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

13.5. Approval of clinical study protocol and amendments

Before the start of the study, the clinical study protocol, informed consent document, and any other appropriate documents will be submitted to the REC, the MHRA and the Sponsor with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities, in accordance with local legal requirements.

Investigational products can only be supplied Sponsor after documentation on all ethical and legal requirements for starting the study has been received by the product provider.

Before the first subject is enrolled in the study, all ethical and legal requirements must be met, including approval of the study by the NHS organisation via the Sponsor Research and Development department, the REC, the MHRA and HRA.

Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should be revised, thus all protocol amendments and administrative changes must first be discussed with and approved by the Sponsor before being submitted to the REC and the MHRA, in accordance with legal requirements.

The Investigator must keep a record of all communication with the REC, the MHRA, and the Sponsor. This also applies to any communication between the Investigator (or the coordinating Investigator, if applicable) and the authorities.

13.6. Protocol amendments

Requests for any amendments to the study must be sent to the Sponsor and R&I QA office by the Chief Investigator or a delegated individual. The Sponsor will determine whether said amendments are substantial or non-substantial prior to their submission to the appropriate bodies for approval. Patients should be re-consented to the study if the amendments affect the information they have received, patient safety, or if the change alters the type or quality of the data collected for the study. Patients should only be re-consented AFTER an amendment has been fully approved.

13.7. Ongoing information for MHRA/REC

In accordance with CTIMP regulations and Sponsor policy, the Investigator (or their delegate) must submit to the MHRA, REC and the Sponsor:

- Information on suspected unexpected serious adverse reactions (SUSARs) from the Investigator's site, as soon as possible and always within 24 hours of the research team becoming aware of them.
- Expedited safety reports, as soon as possible and always within the necessary reporting deadline.
- Development Safety Update Reports (DSUR) to both REC and MHRA (also referred to as Annual Safety Reports).
- Annual reports on the progress of the study to the REC.
- The Declaration of the End of Trial Notification form.

14. FINANCE AND INSURANCE

14.1. Indemnity and insurance

The University of Leeds is able to provide insurance to cover for liabilities and prospective liabilities arising from negligent harm. In certain circumstances, we provide insurance cover for claims arising from non-negligent harm.

Clinical negligence indemnification will rest with The Leeds Teaching Hospitals NHS Trust under standard NHS arrangements.

Further details of liability and insurance provisions for this study are given in separate agreements.

14.2. Financial disclosure

None of the investigators or members of the research team have any financial involvement with the sponsorship or funding bodies or will receive personal benefits, incentives or payment over and above normal salary.

15. PUBLICATION

The trial will be registered with an authorised registry, according to ICMJE Guidelines, prior to the start of recruitment.

The success of the trial depends upon the collaboration of all patients. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributor ship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to: Conception and design, or acquisition of data, or analysis and interpretation of data, page drafting the article or revising it critically for important intellectual content, and final approval of the version to be published, and that all these conditions must be met (www.icmje.org).

In light of this, the Chief Investigator, and relevant staff will be named as authors in any publication. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial.

To maintain the scientific integrity of the trial, data will not be released prior to the end of the trial, either for trial publication or oral presentation purposes, without the permission of the Trial Steering Committee or the Chief Investigator. In addition, individual collaborators must not publish data directly relevant to the questions posed in the trial until the main results of the trial have been published and following written consent from the Sponsor.

16. REFERENCES

1. Peluso, G., et al., *Clinical and ultrasonographic remission determines different chances of relapse in early and long standing rheumatoid arthritis.* Ann Rheum Dis, 2011. **70**(1): p. 172-5.
2. Katchamart, W., et al., *Predictors for Remission in Rheumatoid Arthritis Patients: A Systematic Review.* Arthritis Care & Research, 2010. **62**(8): p. 1128-1143.
3. Scott, D.L., F. Wolfe, and T.W. Huizinga, *Rheumatoid arthritis.* Lancet, 2010. **376**(9746): p. 1094-108.
4. Emery, P., et al., *Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial.* Lancet, 2008. **372**(9636): p. 375-82.
5. Saleem, B., et al., *Patients with RA in remission on TNF blockers: when and in whom can TNF blocker therapy be stopped?* Ann Rheum Dis, 2010. **69**(9): p. 1636-42.
6. Smolen, J.S., et al., *EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update.* Ann Rheum Dis, 2014. **73**(3): p. 492-509.
7. Smolen, J.S., et al., *EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update.* Annals of the Rheumatic Diseases, 2013.
8. Hyrich, K.L., et al., *Comparison of the response to infliximab or etanercept monotherapy with the response to cotherapy with methotrexate or another disease-modifying antirheumatic drug in patients with rheumatoid arthritis - Results from the British Society for Rheumatology Biologics Register.* Arthritis and Rheumatism, 2006. **54**(6): p. 1786-1794.
9. Hyrich, K.L., et al., *Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register.* Rheumatology, 2006. **45**(12): p. 1558-1565.
10. Burmester, G.R., et al., *Clinical remission and/or minimal disease activity in patients receiving adalimumab treatment in a multinational, open-label, twelve-week study.* Arthritis & Rheumatism-Arthritis Care & Research, 2008. **59**(1): p. 32-41.
11. Emery, P., et al., *Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. .* Lancet. , 2008. **372**: p. 375-382.
12. Emery, P., et al., *Very early (< 4 months) treatment with combination etanercept and methotrexate produces significantly better remission rates: results from the COMET study [abstract]. .* Ann Rheum Dis. , 2010. **69**(Suppl3): p. S57.
13. Pease, C.T., et al., *Does the age of onset of rheumatoid arthritis influence phenotype? a prospective study of outcome and prognostic factors.* Rheumatology, 1999. **38**(3): p. 228-234.
14. Verstappen, S.M.M., et al., *A good response to early DMARD treatment of patients with rheumatoid arthritis in the first year predicts remission during follow up.* Annals Of The Rheumatic Diseases, 2005. **64**(1): p. 38-43.
15. Forslind, K., et al., *Sex: a major predictor of remission in early rheumatoid arthritis?* Annals Of The Rheumatic Diseases, 2007. **66**(1): p. 46-52.
16. Ponchel, F., et al., *An immunological biomarker to predict MTX response in early RA.* Annals of the Rheumatic Diseases, 2014. **73**(11): p. 2047-2053.
17. *European Medicines Agency. Benepali.* 2016; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004007/smops/Positive/human_smop_000900.jsp&mid=WC0b01ac058001d127.
18. van der Heijde, D.M., et al., *Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score.* Ann Rheum Dis, 1990. **49**(11): p. 916-20.
19. van der Heijde, D.M., et al., *Validity of single variables and composite indices for measuring disease activity in rheumatoid arthritis.* Ann Rheum Dis, 1992. **51**(2): p. 177-81.

20. Hunt L, H.E., Nam J, et al., *T cell subsets: an immunological biomarker to predict progression to clinical arthritis in ACPA-positive individuals.* Ann Rheum Dis, 2015.
21. Fries, J.F., P.W. Spitz, and D.Y. Young, *The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales.* J Rheumatol, 1982. **9**(5): p. 789-93.
22. B, S., ed. *Ramey D, Fries J, Singh G. The Health Assessment Questionnaire 1995 — status and review.* 2nd ed. Quality of life and pharmacoeconomics in clinical trials. 1995, Lippincott-Raven: Philadelphia 227-37.
23. Kirwan, J.R. and J.S. Reeback, *Stanford Health Assessment Questionnaire modified to assess disability in British patients with rheumatoid arthritis.* Br J Rheumatol, 1986. **25**(2): p. 206-9.
24. Aletaha, D., et al., *2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative.* Arthritis Rheum, 2010. **62**(9): p. 2569-81.
25. Smolen, J.S., et al., *A simplified disease activity index for rheumatoid arthritis for use in clinical practice.* Rheumatology (Oxford), 2003. **42**(2): p. 244-57.

Appendix 1

Scale for interpreting T-cell results based on age

"Patients' naïve T-cell frequency (%) will be compared to the level expected for their age according to the following formula derived from 106 healthy controls: (-0.54*age) + 63.19.
A patient whose naïve T-cell level is at or above this value will be considered to have a normal T-cell result; a patient with levels below the age-expected value will be considered to have an abnormal result."

Age	Normality Threshold		Age	Normality Threshold
18	53.47		60	30.79
19	52.93		61	30.25
20	52.39		62	29.71
21	51.85		63	29.17
22	51.31		64	28.63
23	50.77		65	28.09
24	50.23		66	27.55
25	49.69		67	27.01
26	49.15		68	26.47
28	48.07		69	25.93
29	47.53		70	25.39
30	46.99		71	24.85
31	46.45		72	24.31
32	45.91		73	23.77
33	45.37		74	23.23
34	44.83		75	22.69
35	44.29		76	22.15
36	43.75		77	21.61
37	43.21		78	21.07
38	42.67		79	20.53
39	42.13		80	19.99
40	41.59		81	19.45
41	41.05		82	18.91
42	40.51		83	18.37
43	39.97		84	17.83
44	39.43		85	17.29
45	38.89		86	16.75
46	38.35		87	16.21
47	37.81		88	15.67
48	37.27		89	15.13
49	36.73		90	14.59
50	36.19		91	14.05
51	35.65		92	13.51
52	35.11		93	12.97
53	34.57		94	12.43
54	34.03		95	11.89
55	33.49		96	11.35
56	32.95		97	10.81
57	32.41		98	10.27
58	31.87		99	9.73
59	31.33			