PROTOCOL

JRMO Research Protocol for MHRA Regulated Studies

Full Title	**The 3TR Molecular PAthobiology and PRecision Therapy iN EaRly Rheumatoid Arthritis Study**
Short Title	**3TR-PARTNER-RA Study**
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I. Contents

Contents

II. Glossary of terms and abbreviations

AE	Adverse Event
ALT	Alanine Transaminase
Anti-CCP	Anti-citrullinated Protein Antibody
AST	Aspartate Transaminase
bDMARD	Biological Disease Modifying Anti-Rheumatic Drugs
CI	Chief Investigator
CRF	Case Report Form
CRP	C-reactive Protein
csDMARD	Conventional Synthetic Disease Modifying Anti-Rheumatic Drugs
DMARD	Disease Modifying Anti-Rheumatic Drugs
EMR	Experimental Medicine & Rheumatology
ESR	Erythrocyte Sedimentation Rate
IA	Inflammatory Arthritis
ICF	Informed Consent Form
ISRs	Injection Site Reactions
JRMO	Joint Research Management Office
NHS	National Health Service
NRES	National Research Ethics Service
Participant	An individual who takes part in a clinical study
PI	Principal Investigator
PIS	Participant Information Sheet
PsA	Psoriatic Arthritis
RA	Rheumatoid Arthritis
REC	Research Ethics Committee
RF	Rheumatoid Factor
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
TMG	Trial Management Group
UA	Undifferentiated Arthritis
US	Ultrasound
VAS	Visual Analogue Score
wk(s)	Week(s)

III. Signature page

Chief Investigator Agreement

The study as detailed within this research protocol will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, the Declaration of Helsinki, and the current regulatory requirements, including the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and all subsequent amendments. I delegate responsibility for the statistical analysis and oversight to a qualified statistician (see declaration below).

Chief Investigator name: Professor Costantino Pitzalis

Signature: 

Date: 27/01/2025

Lead Statistician's Agreement

The study as detailed within this research protocol plan will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, the Declaration of Helsinki, and the current regulatory requirements, including the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and all subsequent amendments, and ICH E9 - Statistical principles for Clinical Trials and ICH E10 - Choice of Control Groups.

I take responsibility for ensuring the statistical work in this protocol is accurate, and for the statistical analysis and oversight of this study.

Statistician's name: Rhian Gabe

Signature: 

Date: 16/01/2025

Principal Investigator Agreement Page

The clinical study as detailed within this research protocol **(Version XXX, dated XX XXX XX)**, or any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the UK Policy Framework for Health and Social Care Research, the World Medical Association Declaration of Helsinki (1996), Principles of ICH-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.

Principal Investigator Name: _____

Principal Investigator Site: _____

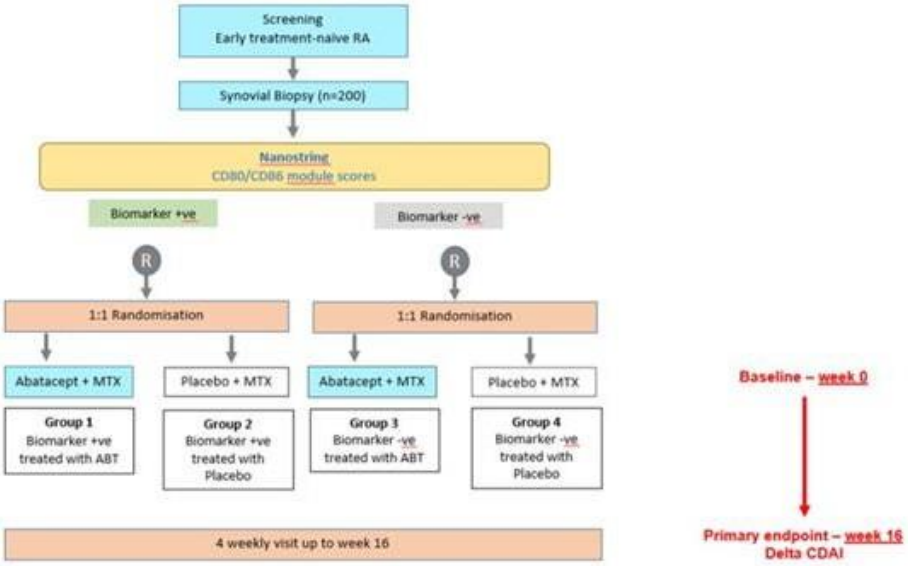
Signature: _____

Date: _____

IV. Synopsis

Full title	The 3TR Molecular PAthobiology and PRecision Therapy iN EaRly Rheumatoid Arthritis Study
Short title and / or acronym	3TR-PARTNER-RA study
Sponsor	Queen Mary University of London
Study design and methodology	Double-blinded, randomised controlled, international multi-centre clinical trial
Phase of the trial	IV
MHRA Risk level	Type A
Study setting	Multi-site, International trial
Investigational Medicinal Product(s)	Abatacept (ORENCIA) 125 mg solution for injection in pre-filled syringe Matching Placebo of active Abatacept prefilled syringe
Medical condition or disease under investigation	Rheumatoid arthritis
Inclusion and exclusion criteria	**Inclusion criteria** 1. Adults (female and male) aged 18 or over. 2. Willing and capable of giving informed consent. 3. 2010 ACR / EULAR classification criteria for a diagnosis of Rheumatoid Arthritis* 4. Symptom duration of <12 months 5. At least one swollen joint, which is amenable to synovial biopsy (minimum grade 2 synovial thickening, as assessed at the biopsy visit). 6. Moderate and severe Disease Activity (DAS28>3.2) 7. No prior DMARD therapies (conventional, targeted or biologic DMARDs) 8. Patient is judged by the supervising clinician to be a suitable candidate based upon medical history, physical examination, vital signs, and routine laboratory tests. 9. Willing and able to comply with scheduled visits, laboratory tests, and other study procedures. ** The ACR/EULAR classification for a diagnosis of RA could have been at any time in the patient's disease history; the score does not need to be 6 or more at screening.* **Exclusion Criteria** 1. Patients unable to tolerate synovial biopsy or in whom this is contraindicated including patients on anti-coagulants (e.g. warfarin). Patients on short-acting direct oral anticoagulant agents can be considered when anti-coagulant can be temporarily stopped, in line with local guidelines for procedures with a low risk of bleeding, taking into account the individual thromboembolic risk. Oral anti-platelet

	agents are permitted. 2. Patients in whom there is no suitable joint for biopsy. 3. Hypersensitivity to the active substance or to any of the excipients of abatacept or methotrexate, or any other contraindications to the study medications, as per the current SmPC. 4. History of or current primary inflammatory joint disease or primary rheumatological autoimmune disease other than RA (if secondary to RA, then the patient is still eligible). 5. Prior exposure to any conventional/biologic/targeted DMARDs for RA 6. Treatment with any investigational agent ≤ 8 weeks prior to baseline or < 5 half-lives of the investigational drug (whichever is the longer) 7. Intra-articular or parenteral corticosteroids, or oral prednisolone more than 10mg/d or equivalent ≤ 4 weeks prior to screening visit. 8. Patients with a serious underlying medical disorder (e.g., end stage renal disease). 9. Active infection 10. Subject has a history or known presence of recurrent or chronic infection (eg, hepatitis B virus [HBV], hepatitis C virus [HCV], human immunodeficiency virus HIV]; recurrent urinary tract infections are allowed. 11. Subjects testing positive for acute or chronic hepatitis A, B, or C, unless they are indicative of prior hepatitis B vaccination or cured hepatitis A or B and accompanied by normal liver transaminase values. 12. Septic arthritis of a native joint within the last 12 months 13. Septic arthritis of a prosthetic joint within 12 months or indefinitely if the joint remains in situ 14. Latent TB infection unless they have completed adequate antibiotic prophylaxis 15. Receipt of live vaccine <3 months prior to first dose of study medication 16. Major surgery in 3 months prior to first dose of study medication 17. Presence of a transplanted organ (with the exception of a corneal transplant >3 months prior to screening). 18. Known recent substance abuse (drug or alcohol). 19. Patients currently recruited to other clinical trials or taking part in a CTIMP study in the previous 4 months. 20. Other severe acute or chronic medical or psychiatric condition, or laboratory abnormality that would impart, in the judgment of the investigator, excess risk associated with study participation or study drug administration, or which, in the judgment of the investigator, would make the patient inappropriate for entry into this study. This should include assessment of risk factors for known clinically important risks associated with a study drug. 21. Patients with severe hepatic impairment (Child Pugh C classification). 22. Patients that are primary or secondary immunodeficiency (history of or currently active). 23. Poor tolerability of venepuncture or lack of adequate venous access for required blood sampling during the study period. 24. Women who are pregnant or breast-feeding. 25. Women of child-bearing potential or males whose partners are women of child-bearing potential, unwilling to use an effective method

	of contraception (recommend double contraception) throughout the trial and beyond the end of trial treatment for the duration as defined in the relevant SmPC. 26. Individuals who are unable to give informed consent for any reason (vulnerable groups).
Planned number of participants	200 randomised (1:1) patients
Treatment duration	16 weeks
Follow up duration	30 days after last dose of IMP
End of Trial definition	6 months after Last Patient Last Visit (LPLV)
Objectives	The primary objective of this trial is to determine whether synovial molecular profiles can inform treatment response to abatacept in early RA.
Study Flowcharts	

1.0 Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease which, in industrialised countries, affects 0.5-1% of adults, with 5-50 per 100,000 new cases annually[1]. 75% of new diagnoses are in people of working age[2]. The disorder more commonly affects women and elderly people. Uncontrolled active RA causes joint damage, disability, decreased quality of life, and cardiovascular and other comorbidities[1]. It causes destruction to bone and cartilage which leads to significant disability in patients. There are currently many different treatments approved for use in rheumatoid arthritis which have improved prognosis in the last few decades. The first line treatment includes use of conventional synthetic DMARDs (csDMARDs) such as methotrexate, leflunomide, sulfasalazine and hydroxychloroquine. However, despite the treatments available, 40% of patients fail to respond to first-line therapy. Therefore, there remains an unmet clinical need to better understand the immunopathogenesis of early rheumatoid arthritis and define biomarkers for response to treatment.

1.1 Background

A previous observational study performed at the Centre of Experimental Medicine and Rheumatology called the 'Pathobiology of Early Arthritis Cohort' (PEAC) demonstrated the presence of three distinct pathology groups in patients with RA; namely the a) lympho-myeloid b) diffuse-myeloid and c) pauci-immune pathotypes[3]. These pathotypes are characterised by the a) presence of B cells and myeloid cells b) cells of the myeloid lineage but poor in B cells and c) scarce immune cells with a predominance of stromal cells in the synovium respectively. In addition to histological analysis of the synovium, molecular analysis of the synovium was also undertaken by RNA sequencing. The lympho-myeloid phenotype was found to be associated with the highest level of erythrocyte sedimentation rate (ESR), C- reactive protein (CRP), anti-citrullinated protein antibody (ACPA) titre and DAS-28 ESR scores as well as greater erosive disease and a higher 'inflammatory signal on ultrasound. The pauci-immune pathotype on the other hand was associated with the lowest levels of ESR and CRP, rheumatoid factor (RF) and ACPA positivity and US scores despite high DAS-28 ESR scores. At a molecular level, gene expression signatures were found to correlate with response to csDMARD therapy. For example, the myeloid and lymphoid scores were associated with greater response to csDMARDs as measured by larger decreases in DAS28-ESR post-treatment.
Abatacept is indicated for moderate to severe active rheumatoid arthritis (RA) in adult patients who responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate (MTX) or a tumour necrosis factor (TNF)-alpha inhibitor. In this trial DMARD naïve RA patients with <12 months symptom duration will receive MTX + placebo or MTX + abatacept, so abatacept is prescribed "off-label" for patients at this stage of RA disease. Abatacept has been used in a number of early intervention trials and safety and efficacy as an early RA intervention has been demonstrated in the following trials: NORD-STAR[4], AGREE[5] and AVERT[6]. For example, in the NORD-STAR trial, compared with active conventional therapy, CDAI remission rates were significantly higher for abatacept[4]. Additionally, in the trial, the proportion of SAEs was lowest in the abatacept group when compared to certolizumab, tocilizumab and active conventional therapy.

We propose to perform a double-blinded, randomised controlled study of patients newly diagnosed with RA (symptoms <12 months) and fulfilling the 2010 ACR/EULAR classification criteria for RA who will undergo a synovial biopsy at baseline and randomised (1:1) to drug (abatacept) and methotrexate or placebo and methotrexate arm. Half of the patients will receive the drug (abatacept) and methotrexate and the other half will receive placebo and methotrexate. Patients will be followed up to 16 weeks at which point all patients will be offered

a voluntary second synovial biopsy. At the end of the trial, patients randomised to the drug arm and patients randomised to the placebo arm who respond to treatment with a low disease activity or remission will subsequently be managed by their rheumatologist and be offered the opportunity to be followed up as part of the CReMSIA research database whereby patients consent for their clinical information obtained at routine NHS visits to be recorded on a database. Patients randomised to the placebo arm and with high or moderate disease activity will be given the choice of entering the 3TR Precis-The-RA or the 3TR Precis-The-RA Sub-study (3TR Molecular Pathobiology-Driven Precision Therapy in RA), and subsequently be randomised either in the control group where treatment allocation to biologic therapy is random or to the 'treatment allocation according to biomarker group' whereby treatment allocation to a biologic is based on a biomarker if one is identified from the second synovial biopsy.

Investigational Medical Products

Abatacept (ORENCIA) – within the remit of this study abatacept is being used in accordance with its UK license as it is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis. It is only licensed in the UK when patients have failed first line drugs.

Abatacept, a selective co-stimulation modulator, is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T lymphocyte (T cell)-associated antigen 4 (CTLA-4) linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human immunoglobulin G1 (IgG1). Abatacept is produced by recombinant deoxyribonucleic acid (DNA) technology in a mammalian cell expression system.

Abatacept binds to CD80/CD86 receptors on antigen-presenting cells, thereby inhibiting their binding to the costimulatory molecule CD28 on T cells. By inhibiting full T-lymphocyte (T-cell) activation, abatacept also affects the downstream inflammatory cascade.

Abatacept (ORENCIA) is indicated for:

- the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA).
- the treatment of patients 2 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis (pJIA).
- the treatment of adult patients with active psoriatic arthritis (PsA).
- the prophylaxis of acute graft versus host disease (aGVHD), in combination with a calcineurin inhibitor and methotrexate, in adults and pediatric patients 2 years of age and older undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated donor.

Limitations of Use: Concomitant use of Abatacept with other immunosuppressives [e.g., biologic disease-modifying antirheumatic drugs (bDMARDS), Janus kinase (JAK) inhibitors is not recommended.

Preclinical data

The pharmacokinetics of abatacept were studied in healthy adult subjects after a single 10 mg/kg IV infusion and in RA subjects after multiple 10 mg/kg IV infusions. In patients with RA, the apparent volume of distribution at steady state was 0.07 L.

The pharmacokinetics of abatacept showed proportional increases of Cmax and AUC over the dose range of 2 mg/kg to 10 mg/kg. At 10 mg/kg, serum concentration appeared to reach a steady state by day 60 with a mean (range) trough concentration of 24 mcg/mL (1 to 66 mcg/mL). No systemic accumulation of abatacept occurred upon continued repeated treatment with 10 mg/kg at monthly intervals in RA patients.

Abatacept exhibited linear pharmacokinetics following subcutaneous administration. The mean (range) for Cmin and Cmax at steady state observed after 85 days of treatment was 32.5 mcg/mL (6.6 to 113.8 mcg/mL) and 48.1 mcg/mL (9.8 to 132.4 mcg/mL), respectively. The bioavailability of abatacept following subcutaneous administration relative to intravenous administration was 79%. Mean estimates for systemic clearance (0.28 mL/h/kg), volume of distribution (0.11 L/kg), and terminal half-life (14.3 days) were comparable between subcutaneous and intravenous administration.

Clinical data

Abatacept is indicated for the prophylaxis of acute graft versus host disease (aGVHD), in combination with a calcineurin inhibitor and methotrexate, in adults and paediatric patients 2 years of age and older undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated-donor.
The concomitant use of Abatacept with other potent immunosuppressants (e.g., biologic disease-modifying antirheumatic drugs (bDMARDS), Janus kinase (JAK) inhibitors) is not recommended.

Clinical Outcomes

Study IM101550 was a randomized, double-blind clinical trial to evaluate the efficacy and safety of abatacept SC in MTX-naive adults with early RA[7]. The total duration of the study was 132 weeks, including a screening period, followed by a 56-week Induction Period (IP), followed by a De-escalation Period of 52 weeks, followed by a 24-week Optional Open Label Period. Subjects who discontinue study drugs have a 24-week Post-Treatment Follow-up Period.

The primary objective of this study was to compare the clinical efficacy of weekly abatacept in combination with MTX to MTX alone in achieving remission, defined as SDAI < 3.3, at Week 24. The proportion of subjects in SDAI remission at Day 169 was numerically, but not statistically significantly larger in the abatacept + MTX group (21.3%) than in the MTX monotherapy group (16.0%) (p = 0.2359).

The secondary efficacy objective at Week 24 was to compare the efficacy of weekly abatacept + MTX to MTX alone in achieving DAS28-CRP <2.6. A higher proportion of subjects in the abatacept + MTX group (38.7%) compared with the MTX monotherapy group (25.3%) had DAS28-CRP <2.6 at Day 169 (nominal p = 0.0112).

The key efficacy findings at Day 365 included the following:

- The proportion of subjects in the primary analysis population in SDAI remission, defined as a score of < 3.3, was numerically higher in the abatacept + MTX group (29.8%) than in the MTX monotherapy group (15.3%) (nominal p = 0.0021).
- The proportion of subjects in Boolean remission in the cohort 1 analysis population was numerically larger in the abatacept + MTX group (21.5%) than in the MTX monotherapy group (11.6%) (nominal p = 0.0006).

Radiographic outcomes

The mean change from baseline in radiographic progression of joint damage in the cohort 1 analysis population as measured by modified Sharp/van der Heijde total Sharp score (TSS) was numerically larger in the MTX monotherapy group than in the abatacept + MTX group. The mean (SD) change from baseline in TSS was 2.52 (6.205) in the MTX monotherapy group and 0.53 (2.279) in the abatacept + MTX group (nominal p <0.001).

Quality of life outcomes

Improvement in physical function was measured by the Health Assessment Questionnaire Disability Index (HAQ-DI). In the HAQ-DI, Abatacept demonstrated greater improvement from baseline versus placebo in studies where the efficacy of ORENCIA was assessed in patients with an inadequate response to MTX and who were continued on their stable dose of MTX (study II-IV), and versus MTX where the efficacy and safety of ORENCIA were assessed in methotrexate-naïve patients with RA of less than 2 years disease duration (Study VI). In Study SC-1 (which was a randomized, double-blind, double-dummy, non-inferiority study that compared ORENCIA administered subcutaneously to ORENCIA administered intravenously in 1457 patients with moderate to severely active RA, receiving background methotrexate (MTX), and experiencing an inadequate response to methotrexate), improvement from baseline as measured by HAQ-DI at 6 months and over time was similar between subcutaneous and intravenous Abatacept administration.

Health-related quality of life was assessed by the SF-36 questionnaire at 6 months in the above studies. In these studies, improvement was observed in the Abatacept group as compared with the placebo group in all 8 domains of the SF-36 as well as the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

Clinical Safety outcomes

The integrated cumulative safety experience for IV and SC abatacept use in adults with RA extends from ST through LT periods of 16 RA clinical trials, as indicated in Table 5-1. The data contributing to this integrated safety database are from randomized, controlled (either placebo or active comparator), Bristol Myers Squibb (BMS) studies of RA that included at least one abatacept + MTX treatment group in which study drug was administered more than one time[8].

As consistent safety profiles have been observed for SC and IV abatacept[9,10], studies of both IV and SC abatacept were included in the integrated safety database[11].

The integrated safety database includes 7044 subjects receiving IV or SC abatacept for a total exposure of 21994.84 subject years during the cumulative period (ST plus LT open-label). The mean (SD) duration of exposure to abatacept was 40.1 (20.71) months during the cumulative period.

Table 5.4.1-1: Adverse Events Summary During the Double-blind, Placebo-Controlled Period, All Treated Subjects

	Abatacept (N=2653)	Placebo (N=1485)	Total (N=4138)
Deaths	12 (0.5%)	12 (0.8%)	24 (0.6%)
SAEs	331 (12.5%)	174 (11.7%)	505 (12.2%)
Related SAEs	75 (2.8%)	30 (2.0%)	105 (2.5%)
Discontinued due to SAEs	68 (2.6%)	22 (1.5%)	90 (2.2%)
AEs	2334 (88.0%)	1258 (84.7%)	3592 (86.8%)
Related AEs	1311 (49.4%)	680 (45.8%)	1991 (48.1%)
Discontinued due to AEs	138 (5.2%)	55 (3.7%)	193 (4.7%)
Infections	1440 (54.3%)	767 (51.6%)	2207 (53.3%)
Malignancies	31 (1.2%)	14 (0.9%)	45 (1.1%)
Autoimmune AEs	198 (7.5%)	115 (7.7%)	313 (7.6%)

Includes data up to 56 days or 60 (Phase 2 IV) post last dose in the short-term double-blind period or start of the long-term period whichever occurred first.
Adverse events related to study drug are those with a certain, probable, possible, related or a missing relationship to study drug.
Studies Included: IM101226, IM101063, IM101023, IM101043, IM101031, IM101029, IM101102, IM101101, IM101100
MEDDRA VERSION: 19.0

Table 1: AE Summary from Investigator's Brochure v26.0 22-Dec-2022

1.2 Rationale for study design

Currently, NICE guidelines suggest first-line treatment including use of conventional synthetic DMARDs (csDMARDs) such as methotrexate, leflunomide, sulfasalazine and hydroxychloroquine. However, despite the treatments available, the current failure rate for csDMARD treatment leads to a significant proportion of patients eventually needing biological DMARDs and of these patients, 40% will fail their first biologic TNFi.

In RA, the main limitation of the current "trial and error" approach is the subsequent treatment with drugs targeting different pathways, without knowing if these pathways are expressed in the disease tissue. Therefore, it is important to understand the immune pathways involved in early arthritis to determine whether it is possible to stratify treatment with csDMARDs and subsequent biologic treatment. This study aims to better understand the immune-pathogenesis of early rheumatoid arthritis and define biomarkers for response to treatment.

In recent years, thanks to the development of minimally invasive ultrasound-guided biopsy[12], histological[13] and molecular[14] signatures in the synovial tissue of patients with early RA have been associated with disease outcomes. More specifically, synovial tissue signatures have been shown to stratify response to treatment and predict disease progression, including the development of radiographic damage and, interestingly, the future use of biologics[15].
Recently, the first biopsy-driven Randomised Clinical Trials in RA has shown that the lack of B cell lineage signatures in synovia is associated with lack of response to B cell depleting agent (rituximab) as compared to an alternative medication targeting IL6 receptor (Tocilizumab)[16].

In the case of RA, recent evidence suggesting that, by analogy, the presence of active inflammation in the synovium in the absence / low expression of drug target would result in non-response, as discussed above for the R4RA trial, while high levels of target may favour treatment response. We have identified bDMARDs signatures (transcript modules) prevalent

in discrete patient subpopulations and expressed at higher levels in responder patients, which we used to inform the design of the trial. Thus, we hypothesise that patients lacking any drug target signature (biomarker negative patients) will show lower response rates when compared with biomarker positive patients. To test such a hypothesis, we have developed in collaboration with NanoString custom-made gene expression panels to include the target module signatures that will enable profiling of patients undergoing US- guided biopsy in the trial within 7-10 working days, similarly to the pro-signa assay developed by Nanostring (https://www.prosigna.com/en-gb/).

Participants (randomised to placebo arm) who do not adequately respond to treatment during this study may be eligible to participate in the 3TR-Precis-The-RA sub-study, which will recruit patients who are eligible for anti-TNF therapy. The purpose of the sub-study is to discover if a biopsy at presentation prior to any treatment can be used to determine treatment response even after the patient has received cDMARDs.

The proposed research also has the potential to contribute work of significant clinical advantage for the treatment of RA, with the long-term aim of providing RA patients with the correct treatment the first time and reducing their exposure to drugs that have little or no positive impact on treating their disease. This would provide a measurable positive impact on health economics for patient benefit and the wider NHS.

1.3 Assessment and management of risk

Subjects eligible to take part in the study will be randomised to either abatacept or placebo, both in combination with methotrexate. All patients participating in this trial will receive active therapy for their RA.

Currently, the UK NICE guidelines suggest patients are offered first-line treatment with cDMARD monotherapy using oral methotrexate, leflunomide or sulfasalazine as soon as possible and ideally within 3 months of onset of persistent symptoms. Half of patients in this trial will be randomised to the placebo arm which will be administered in combination with methotrexate therapy.

Abatacept in combination with methotrexate, is indicated for (1) the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate (MTX) or a tumour necrosis factor (TNF)-alpha inhibitor, and (2) the treatment of highly active and progressive disease in adult patients with rheumatoid arthritis not previously treated with methotrexate. In the UK, abatacept in combination with methotrexate is recommended as an option for treating rheumatoid arthritis, only if disease is severe, that is, a disease activity score (DAS28) greater than 5.1, and the disease has not responded to intensive therapy with a combination of conventional disease-modifying antirheumatic drugs (DMARDs). The recommended dose of SC abatacept is 125 mg weekly, regardless of weight. In this trial, half of patients will be randomised to receive abatacept in combination with methotrexate as their first-line therapy.

All patients will undergo synovial biopsies, either US-guided or arthroscopic. These biopsies would not usually be considered routine clinical care. The risks for this type of intervention are small but may include possible infection, bleeding, pain and swelling after the biopsy, and damage to the surrounding tissue such as nerves, tendons or connective tissues. These risks are rare, and the procedure is very well tolerated in most patients. The procedure itself has excellent safety and tolerability and can be applied to both large and small joints as previously demonstrated[17]. The type of biopsy technique performed will be documented for all

participants. Sites with sufficient training and experience in synovial biopsies, will be selected to participate.

Potential Risk of Biopsy:

The majority of patients have no adverse reaction to the procedure and it is generally very well tolerated. Possible complications include infection of the joint or skin, bleeding, pain and rarely nerve or tendon damage (less than 1:10,000 risk).

Risk management:

Infection of joint or skin: biopsy techniques will be performed by trained experts under aseptic techniques to ensure the lowest risk of infection.

Bleeding and pain: Procedures are not performed on patients with known bleeding disorders or anticoagulation therapy. Only minor bleeding has been reported. Simple analgesics will be prescribed to take as required.

Nerve and tendon damage: biopsy techniques will be supervised by trained personnel. Given the ultrasound guided approach, nerve or tendon damage is extremely rare. In the event of nerve or tendon damage the patient will be appropriately treated as per standard hospital practice.

Benefits of participating in the study

Patients may see an improvement in their symptoms of arthritis or may not benefit directly from this study. However, the trial will provide essential information, which could be of benefit to others in the future. Both medications (Abatacept and Methotrexate) within this trial have evidence that they may be effective. This study will find out whether specific RNA signatures enable accurate prediction of what the best treatment will be for rheumatoid patients. It has the potential to be of significant benefit to future patients.

This trial is categorised as a Type A trial as per MHRA risk assessment.

2.0 Trial objectives

2.1 Primary objective(s)

The primary objective of this trial is to determine whether synovial molecular profiles (=drug target signatures) can inform treatment response to abatacept in early RA.

To achieve this objective, we will compare the change in Clinical Disease Activity Index (CDAI) score at 16 weeks between the biomarker positive and the biomarker negative patients within the abatacept group (i.e. Group 1 vs Group 3) Fig.1 Trial Design.

We hypothesise that patients with high synovial immunological infiltrate (lymphoid pathotype) will respond better to abatacept therapy.

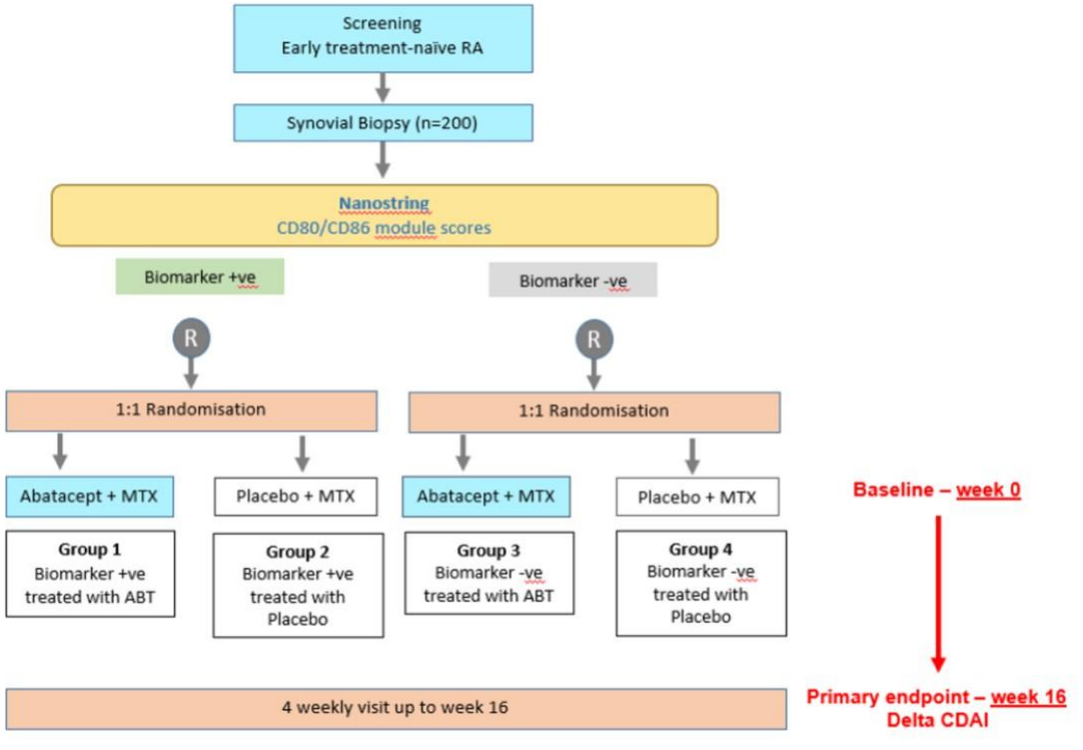


Fig. 1: Trial Design

2.2 Secondary objective(s)

We aim to assess patients treated according to their biomarker: comparing the biomarker-positive patients (as Groups 1 minus 2) vs the biomarker-negative patients (as Groups 3 minus 4).

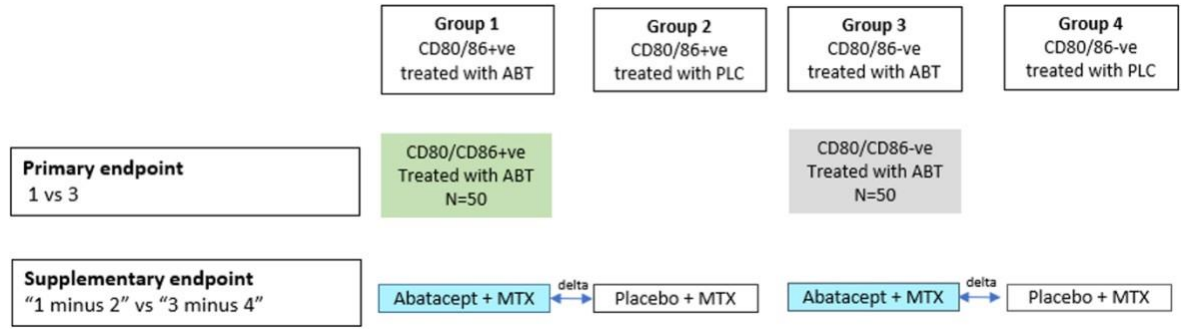


Fig. 2: primary and secondary analyses

2.3 Endpoints

2.3.1 Primary endpoint(s)

The primary endpoint is change CDAI at 16 weeks

2.3.2 Secondary endpoint(s)

1. Percentage of patients with DAS28<3.2 (LDA) at 16 weeks.
2. Percentage of patients deemed responders using American College of Rheumatology 50 (ACR50) measure at 16 weeks.
3. Percentage of patients with CDAI remission at 16 weeks.
4. Change in HAQ-DI at 16 weeks from baseline.
5. Change in SF-36 at 16 weeks from baseline

Secondary endpoints will be reported descriptively within each treatment group.

2.4 Exploratory or tertiary endpoints

1. Percentage of patients deemed responders using American College of Rheumatology 20/70 (ACR20/70) measure at 16 weeks.
2. Percentage of patients with ACR/EULAR Boolean remission at 16 weeks.
3. Mean % change in CDAI score and DAS28 at 16 weeks.
4. Change in FACIT, ESS, and EQ-5D score at 16 weeks from baseline
5. The association between synovial histology and ultrasound measures of inflammation, drug response rates, disease outcome and disability.
6. SAEs from 0 to 16 weeks for all patients
7. Change in 12-max summary measure of US 2D synovial thickness (ST) grey scale and power Doppler (PD) signal from baseline at 16 weeks.
8. Changes from baseline to week 16 in the total histopathological synovitis score.

2.5 Objectives and end points summary

Primary Analysis	Primary Endpoint	Outcome Measure
To determine whether synovial molecular profiles can inform treatment response to abatacept in early RA.	The primary endpoint of the study will be the delta CDAI at 16 weeks	Delta CDAI
Secondary Analyses	**Secondary Endpoint**	**Outcome Measure**
To use alternative outcome measures to assess the robustness of the primary analysis	Percentage of patients with DAS28 ≤2.6 (LDA) at 16 weeks.	DAS28(ESR) ≤2.6
	Percentage of patients deemed responders using American College of Rheumatology 50 (ACR50) measure at 16 weeks.	ACR50
	Percentage of patients with CDAI remission at 16 weeks.	CDAI remission (≤2.8)
	Change in HAQ-DI at 16 weeks from baseline.	HAQ-DI
	Change in SF-36 at 16 weeks from baseline	SF-36

2.6 Study design

This is a multi-site, prospective, randomised double-blinded placebo-controlled clinical trial in patients (female and male 18 years or above) with early symptomatic (≤ 12 months) rheumatoid arthritis who have not commenced DMARD therapy.

Following screening, patients will undergo a synovial biopsy. Possible synovial biopsy sites are the knee, elbow, wrist, shoulder, ankle, MCP, PIP and MTP joints.

Once the biopsy sample has been received by the central laboratory, patients will be stratified into 2 groups, CD80/CD86 positive (biomarker+) or CD80/CD86 negative (biomarker-) and randomised 1:1 to receive either abatacept and methotrexate therapy or placebo and methotrexate therapy.

Patients will attend study visits every 4 weeks and will continue trial treatment until 16 weeks, where the treatment response will be assessed as the primary endpoint.

2.7 Study setting

This is a multi-centre, international trial taking place in the UK and Europe. Patients will be invited to participate when they attend rheumatology clinics and are identified as suitable to start csDMARD therapy. Active trial sites may utilise Participant Identification Centres (PICs) to identify potential participants and refer them to recruiting trial sites for participation in the trial and conduct of all research activities relating to the trial.

3.0 Patient Evaluability and Replacement

3.1 Target Accrual

The trial aims to recruit 200 patients.

3.2 Participant identification and recruitment

Suitable patients will be identified and recruited to the study when they attend participating rheumatology clinics for diagnosis and treatment. Patients will be identified and approached for participation in the trial by their direct care team. In many instances, the research team are integrated into the rheumatology care team at their recruiting site.

If a potential patient cannot speak the native language of the country interpreters should be made available through the hospital translation service. The consent process should be clearly documented in the patient's medical notes, and it must be clear that the trial was adequately explained, and the patient was able to give informed consent. A translator should be available for each patient visit, and this should be clearly documented in the patient notes. If a translator is not available, the patient should not be recruited to the trial.

4.0 Informed consent procedures

Informed consent will be obtained prior to the participant undergoing procedures that are specifically for the purposes of the study and are outside standard, routine care at participating sites. This includes collection of identifiable participant data for the sole purpose of the trial.

The Principal Investigator (PI) has overall responsibility for the informed consent of participants at their site and will ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained, and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP), and Declaration of Helsinki. Informed consent can be delegated to other suitable trained clinicians in this trial and details of any delegation will be documented in the site delegation log.

The right of a participant to refuse participation without giving reasons will be respected. The participant will remain free to withdraw at any time from the study without giving reasons and without prejudicing their further treatment and will be provided with a contact point where they may obtain further information about the study. Where a participant is required to re-consent (for example if new Research Safety Information becomes available during the study, or following an amendment that affects the participant, or new information needs to be provided to a participant) it is the responsibility of the PI to ensure this is done in a timely manner and prior to the next dose of IMP (where applicable).

Patients who are candidates for the study will receive a Patient Information Sheet (PIS), which explains the purpose of the trial, highlights any risks and benefits of participation, and answers frequently asked questions. Patients should be informed during the consent process that if their biopsy sample is of insufficient quality to undergo analysis, they will be withdrawn from further participation in the trial without financial penalty and continue to receive treatment as per standard routine care. There will not impact on standard care if withdrawn.

Participants must be given a minimum of 24 hours to read, review and understand the PIS and must have the opportunity to ask the PI or delegated clinician any questions relating to the study. Following this, the participant must sign the Informed Consent Form (ICF) in the presence of the PI or delegated clinician, who must then countersign the ICF.

Written consent must be obtained, utilising the current approved version of the consent form, prior to any study-specific procedures being performed, (unless already performed as part of routine care, e.g., routine blood). At the time of consent, participants must be informed that they have the right to withdraw their participation in the study, and also their samples, at any stage and that doing so will not affect their future clinical management and care.

The original signed ICF will be filed in the investigator site file (ISF), a copy of the consent form will be given to the participant, and a copy filed in the patient medical notes.

The written consent procedure must be performed by a qualified clinician, who has been delegated consent duties by the PI. The process of obtaining written consent, including the version of the PIS and ICF given to the patient, the dates and who obtained consent must be clearly documented in the patient's medical notes.

4.1 Vulnerable Participant Considerations

Vulnerable groups will not be recruited to this trial.

4.2 Writing, Reading, and Translation Considerations

If a potential patient cannot speak the native language of the country interpreters should be made available through the local hospital translation service. The consent process should be clearly documented in the patient's medical notes, and it must be clear that the trial was adequately explained, and the patient was able to give informed consent. A translator should be available for each patient visit, and this should be clearly documented in the patient notes. If a translator is not available, the patient should not be recruited to the trial.

4.3 Consent for Ancillary Studies

Participants will be asked to consent to their samples being transferred to EMR Biobank (license number 12199) at Queen Mary University under the Human Tissue Act 2014 after their participation in the trial. This will be clearly explained in the PIS. Participants will be asked to explicitly consent to this on the consent form. There is also a separate consent form for the additional and not mandatory biopsy at week 16.

Stool, urine and saliva collection

As part of the 3TR consortium there are wider objectives spanning all the disease areas. The optional stool, urine and saliva samples will be used for future research, and the analysis of these samples is not included in the objectives of the 3TR PARTNER-RA trial, but is a wider objective of the 3TR consortium. The stool, urine and saliva collection is optional, and if a patient would like to donate these samples, they will need to initial a separate point on the Informed consent form (ICF). This will be clearly explained to the participant during the consent process. The samples may be used for projects involving both academic and commercial partners.

4.3.1 Stool Collection (Optional)

When consented to the 3TR-PARTNER-RA study, participants will be asked to donate stool samples, which will be used as part of 3TR research, outside of this trial. This is optional and if a participant wishes to donate stool samples, they will be asked to initial a separate point on the consent form. The samples will be sent by a reputable licensed courier to 3TR consortium partners: the Institute of Clinical Molecular Biology at Kiel University and/or Andalusian Public Health System Biobank, Centro de Investigación Biomédica, Avda. del Conocimiento s/n, 18016, Granada, Spain. .

4.3.2 Urine Collection (Optional)

When consented to the 3TR-PARTNER-RA study, participants will be asked to donate urine samples, which will be used as part of 3TR research, outside of this trial. This is optional and if a participant wishes to donate urine samples, they will be asked to initial a separate point on the consent form. The samples will be centrifuged and stored at -80C at the local site, then will be sent by a reputable licensed courier to a 3TR consortium partner: Andalusian Public Health System Biobank, Centro de Investigación Biomédica, Avda. del Conocimiento s/n, 18016, Granada, Spain, in batches.

4.3.3 Saliva Collection (Optional)

When consented to the 3TR-PARTNER-RA study, participants will be asked to donate saliva samples, which will be used as part of 3TR research, outside of this trial. This is optional and if a participant wishes to donate saliva samples, they will be asked to initial a separate point on the consent form. The samples will be stored at -80C at the local site, and then will be sent by reputable licensed courier to a 3TR consortium partner: Andalusian Public Health System Biobank, Centro de Investigación Biomédica, Avda. del Conocimiento s/n, 18016, Granada, Spain, in batches.

4.4 Consent for Pregnant Partners of Study Participants (Optional)

Not all risks and side effects are known for the treatment of abatacept. It is unknown if abatacept can pass from the bloodstream into semen or whether they have any effects on sperm, pregnancy, or a baby before or after birth. Therefore, if a participant's partner becomes pregnant whilst or after (up to 14 weeks after the last dose of abatacept) the partner is participating in the trial, pregnant partner will be asked to consent for the clinical team to collect information about their health and their pregnancy. This is optional and if pregnant partner agrees, clinical team will contact them after they have given birth to your baby asking you about their pregnancy and delivery and the health of their baby.
The following information will be recorded:

- Relevant medical history
- Details of any previous pregnancies, including outcome and any complications
- Details about this pregnancy
- Any drugs that you are taking during this pregnancy
- The outcome of this pregnancy
- Details about the birth and your baby

Men with partners of childbearing potential will be reminded to use an acceptable and effective method of contraception during the study period and the appropriate time period after stopping study treatment (up to 14 weeks after the last dose of abatacept).

5.0 Participant allocation

Randomisation will take place when all the screening procedures and the biopsy visit are complete and the patient is confirmed eligible for enrolment in the study.

The local Principal Investigator/research nurse must log in to the secure 24-hour automated web-based Early RA 3TR database (https://era3tr.whri.qmul.ac.uk) and complete Screening and Biopsy visit (visits 1 and 2) electronic CRFs prior to randomisation, supplied by Webclinica. The Trial Office will then confirm eligibility once the result of the biopsy analysis has been completed and the result recorded. Randomization will occur through an Interactive Response Technology (IRT) system. The IRT system will generate the randomization number and the randomization number will be captured by and integrated into the electronic data capture system. All participants will be centrally assigned to randomized study intervention using an IRT. Before the study is initiated, the log-in details, telephone number and call-in directions for the IRT will be provided to each site.

All patients with sufficient RNA for analysis will be stratified according to the biopsy result and will be randomised (1:1 allocation ratio) into the abatacept arm or the placebo arm.

Randomisation procedures are detailed in the 3TR-PARTNER-RA Trial Randomisation Specification form.

6.0 Participant eligibility criteria

6.1 Inclusion criteria

1. Adults (female and male) aged 18 or over.
2. Willing and capable of giving informed consent.
3. 2010 ACR / EULAR classification criteria for a diagnosis of Rheumatoid Arthritis. *
4. Symptom duration of <12 months
5. At least one swollen joint, which is amenable to synovial biopsy (minimum grade 2 synovial thickening, as assessed at the biopsy visit).
6. Moderate and severe Disease Activity (DAS28>3.2)
7. No prior DMARD therapies (conventional, targeted or biologic DMARDs)
8. Patient is judged by the supervising clinician to be a suitable candidate based upon medical history, physical examination, vital signs, and routine laboratory tests.
9. Willing and able to comply with scheduled visits, laboratory tests, and other study procedures.

** The ACR/EULAR classification for a diagnosis of RA could have been at any time in the patient's disease history; the score does not need to be 6 or more at screening.*

6.2 Exclusion criteria

1. Patients unable to tolerate synovial biopsy or in whom this is contraindicated including patients on anti-coagulants (e.g. warfarin). Patients on short-acting direct oral anticoagulant agents can be considered when anti-coagulant can be temporarily stopped, in line with local guidelines for procedures with a low risk of bleeding, taking into account the individual thromboembolic risk. Oral anti-platelet agents are permitted.
2. Patients in whom there is no suitable joint for biopsy.

3. Hypersensitivity to the active substance or to any of the excipients of abatacept or methotrexate, or any other contraindications to the study medications, as per the current SmPC.
4. History of or current primary inflammatory joint disease or primary rheumatological autoimmune disease other than RA (if secondary to RA, then the patient is still eligible).
5. Prior exposure to any biologic/targeted DMARDs for RA
6. Treatment with any investigational agent ≤ 8 weeks prior to baseline or < 5 half-lives of the investigational drug (whichever is the longer)
7. Intra-articular or parenteral corticosteroids, or oral prednisolone more than 10mg/d or equivalent ≤ 4 weeks prior to screening visit.
8. Patients with a serious underlying medical disorder (e.g., end stage renal disease).
9. Active infection
10. Subject has a history or known presence of recurrent or chronic infection (eg, hepatitis B virus [HBV], hepatitis C virus [HCV], human immunodeficiency virus HIV]; recurrent urinary tract infections are allowed.
11. Subjects testing positive for acute or chronic hepatitis A, B, or C, unless they are indicative of prior hepatitis B vaccination or cured hepatitis A or B and accompanied by normal liver transaminase values.
12. Septic arthritis of a native joint within the last 12 months
13. Septic arthritis of a prosthetic joint within 12 months or indefinitely if the joint remains in situ
14. Latent TB infection unless they have completed adequate antibiotic prophylaxis
15. Receipt of live vaccine <3 months prior to first dose of study medication
16. Major surgery in 3 months prior to first dose of study medication
17. Presence of a transplanted organ (with the exception of a corneal transplant >3 months prior to screening).
18. Known recent substance abuse (drug or alcohol).
19. Patients currently recruited to other clinical trials or taking part in a CTIMP study in the previous 4 months.
20. Other severe acute or chronic medical or psychiatric condition, or laboratory abnormality that would impart, in the judgment of the investigator, excess risk associated with study participation or study drug administration, or which, in the judgment of the investigator, would make the patient inappropriate for entry into this study. This should include assessment of risk factors for known clinically important risks associated with a study drug.
21. Patients with severe hepatic impairment (Child Pugh C classification).
22. Patients that are primary or secondary immunodeficiency (history of or currently active).
23. Poor tolerability of venepuncture or lack of adequate venous access for required blood sampling during the study period.
24. Women who are pregnant or breast-feeding.
25. Women of child-bearing potential or males whose partners are women of child-bearing potential, unwilling to use an effective method of contraception (recommend double contraception) throughout the trial and beyond the end of trial treatment for the duration as defined in the relevant SmPC.
26. Individuals who are unable to give informed consent for any reason (vulnerable groups).

7.0 Study Schedule

7.1 Schedule of treatment for each visit

7.2 Schedule of assessment (in diagrammatic format)

Visit number	**1**	**2[m]**	**3**	**4**	**5**	**6**	**7**	**Post treatment visit/call**
Timeline (weeks)	**-6 to -1**	**-3 to -1**	**0**	**4**	**8**	**12**	**16**	**30 or more days after visit 7**
Deviation window (days from scheduled visit)	**N/A**			**+/- 7 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**	**N/A**
Visit type	**Screening**	**Biopsy & Randomisation[m]**	**Baseline**	**Treatment Phase**				**Follow up**
ENROLLMENT PROCEDURES								
Informed Consent	X							
Inclusion and Exclusion Criteria	X							
Demographics	X							
Medical History[f]	X							
MEDICAL PROCEDURES								
Concomitant Medication review	X	X	X	X	X	X	X	
RF & CCP[a]	X							

ACR Criteria	X							
Pregnancy test[k]	X		X	X	X	X	X	
Chest X-ray[j]	X							
ECG	X							
Hepatitis serology, HIV, IGRA[i]	X							
Physical Examination	X		X	X	X	X	X	
Cardiovascular risk profile	X							
Weight and Height	X		X	X	X	X	X	
Vital Signs (BP, pulse, temp.)	X		X	X	X	X	X	
Haematology, biochemistry panel, ESR, CRP[b][c]	X		X	X	X	X	X	
DISEASE ACTIVITY ANALYSIS								
Joint Assessment (66/68)[l]	X		X	X	X	X	X	
X-ray Hands & Feet[h]			X				X	
CDAI	X		X	X	X	X	X	
DAS28	X		X	X	X	X	X	
VAS Pain Score	X		X	X	X	X	X	
HAQ Questionnaire			X	X	X	X	X	
TREATMENT PROCEDURES								
Randomisation[g]		X						
Commencement of randomised treatment			X					
Dispensing of randomised treatment			X	X	X	X		
Adverse Events		X	X	X	X	X	X	X

Study Bloods		X		X	X	X	X	
Ultrasound[d]		X[d]					X[d]	
Pre-biopsy Assessment		X					X[e]	
Synovial Biopsy[e]		X					X[e]	
Post-biopsy Assessment			X					X[e]
Stool collection (optional)		X		X			X	
Urine collection (optional)		X		X			X	
Saliva collection (optional)		X		X			X	
PATIENT REPORTED OUTCOMES								
FACIT-fatigue Questionnaire			X	X		X	X	
SF-36			X	X		X	X	
Epworth Sleepiness scale			X	X		X	X	
EQ-5D-5L			X	X		X	X	

a. RF/CCP tests should be performed unless these tests have been done previously and do not need repeating as per local guidelines
b. At screening visit - routine blood tests do not need to be taken if the patient has already had all routine blood tests performed within 3 weeks of the screening visit.
At biopsy visit – routine bloods do not need to be taken if the patient has already had routine bloods performed at the screening visit and within 3 weeks of the biopsy visit.
c. ESR, CRP, Haematology (Hb, Haematocrit, WBC, platelet count, neutrophils, lymphocytes, Red blood cell count, Mean cell haemoglobin, Mean cell volume), Biochemistry (Urea, sodium, Creatinine, potassium, ALT, AST).
d. The US assessment at visit 2 will also include the joint selected for biopsy to ensure that there is sufficient thickening to meet the following inclusion criterion: selected joint for biopsy must be a minimum grade 2 synovial thickening, as assessed at the biopsy visit. This is essential for all patients participating in the trial. Full ultrasound assessments may be optional at some participating sites and should include a full set of MCPs and wrist joints-please refer to the ultrasound manual.
e. Assessment and feasibility at visit 7 will be performed. Patients will be asked to consent or opt out. Synovial fluid should also be collected, where possible. Visit 2 biopsy is compulsory for participation in the study. If a participant does not undergo a biopsy at visit 2 for any reason, they will be withdrawn from the study.
f. Including covid-19 history/vaccine status, allergies, and 3TR Disease & other Specific Co-Morbidities.
g. Randomisation will be performed by the central coordinating office on completion of visits 1 and 2 and on receipt of the biopsy at the central laboratory.
h. Alternatively; X-ray of hands and feet may be performed at visit 2 prior to the biopsy. Plain X-rays of hands and feet do not need to be taken if the patient has already had them done within 8 weeks of the baseline visit, as per the imaging manual.
i. Hepatitis B, TB (IGRA), Hepatitis C, and HIV screening must be performed unless it has been done in the preceding 3 months of the screening visit or in line with local practice.

j. A chest X-ray must be performed as screening for tuberculosis prior to biological therapy. A chest x-ray must be done at the screening visit to confirm the patient's eligibility unless a chest X-ray has been done in the preceding 3 months of the screening visit and the patient must not have had any pulmonary symptoms since then. The total protocol dose is less than 0.03mSv. This is equivalent to a few days of average natural background radiation in the UK.
k. A pregnancy test will be performed at each study visit for female patients of childbearing age irrespective of the use of contraceptive methods.
l. Joint assessments and VAS physician assessments to be completed by the nominated 'blinded joint assessor'. Joint assessments and VAS physician assessment are only required to be completed by the blinded joint assessor from the baseline visit onwards.
m. Visit 2 (biopsy visit) may be combined with the completion of visit 1 (study screening visit) if all screening procedures and results are available prior to the biopsy, and the patient is confirmed eligible for enrolment into the study. Sites should contact the coordinating office before arranging.

7.3 Randomisation Method and Procedure

Once the biopsy sample has been received by the central laboratory, patients will be stratified into 2 groups, CD80/CD86 positive (biomarker+) or CD80/CD86 negative (biomarker-) and randomised 1:1 to receive either abatacept and methotrexate therapy or placebo and methotrexate therapy.

Randomisation will take place when all the screening procedures and the biopsy visit are complete, and the biopsy has been received by the central laboratory.

The local site staff (Principal Investigator/research nurse) must log in to the secure 24-hour/7 day automated Early RA 3TR database for the 3TR-PARTNER-RA study (https://era3tr.whri.qmul.ac.uk) with the Data Safe Heaven (ITS) as backup and complete Screening and Biopsy visit (visits 1 and 2) electronic CRFs prior to randomisation. In the rare event that the 3TR-PARTNER-RA database (Early RA 3TR) is not accessible, paper CRFs may be submitted to perform the randomisation. The 3TR-PARTNER-RA Trial Office will then confirm eligibility and perform randomisation.
The Coordinating Trial Office will then confirm eligibility based on the data recorded, and once the result of the biopsy analysis has been received from the central laboratory the randomisation will be performed.

The randomisation in the study will be applied using simple randomisation by the 3TR Trials office, with an equal allocation ratio. All patients with sufficient RNA for analysis will be randomised using simple randomisation (1:1 allocation ratio) into the drug or placebo arm according to biomarker arms (positive or negative biomarker).

The randomisations list will be prepared by the Trial Statistician and securely stored in a separate table within the Early RA 3TR database back-end so that it is not accessible to end users or anyone else than a limited number of information support staff who have access to all systems. Once a participant has been allocated an arm, there is an audit trail that prevents anyone from changing the allocation or pretending that no allocation has been made.

Before the study is initiated, the log-in details, telephone number and call-in directions for the Early RA 3TR Database for the 3TR-PARTNER-RA study will be provided to each site.

The randomized intervention kit number list is generated centrally by BMS and IMPs are packaged in accordance with this list. The randomization and intervention allocation are performed centrally by the Early RA 3TR Database, which generates the participant randomization list and allocates the intervention number and the corresponding intervention kits to the participants according to it.
A randomized participant is defined as a participant who has been allocated to a randomized intervention regardless of whether the intervention kit was used or not (ie, participants registered by the Early RA 3TR Database in the 3TR-PARTNER-RA study).
A participant cannot be randomized more than once in the study.

The result (i.e. randomised treatment arm) will then be filled to the local site staff (each site will have a nominated joint assessor). The local site staff will immediately be able to see the result of the randomisation, however, they will be blinded to any information about the patient's biopsy result.

Randomisation methods and procedures will be described within the Database User Manuals and Data Management Plan.

7.4 Blinding

Neither the participant nor any of the investigators or site staff who are involved in the treatment or clinical evaluation and monitoring of the participants will be aware of the study intervention received.

- The study drug and placebo will be provided in blinded treatment kit numbers obtained through the Early RA 3TR Database. Abatacept 125 mg and placebo matching will be provided in identically matched prefilled syringes that are visually indistinguishable. Syringes and boxes will be labelled with a kit number.
- Unblinded personnel will include designated representative(s) from the Sponsor or QMUL-designed personnel to review unblinded data.
- Blinded personnel will include designated representative(s) from the study site, and Sponsor. Administration of the study drug will be completed by blinded study site personnel. The study drug will be administered in the same manner to maintain the blindness of the treatment allocation.

The randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization. The investigator documents and reports the action to the Sponsor, without revealing the treatment given to the participant to the Sponsor staff.
The Sponsor retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational medicinal product and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

7.4.1 Procedures for Unblinding

The Early RA 3TR Database for the 3TR-PARTNER-RA study will be programmed with blind-breaking instructions. In case of an emergency, the Investigator, as the doctor responsible for the treatment, has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator may, at the Investigator's discretion, contact the Sponsor to discuss the situation prior to unblinding a participant's treatment assignment unless this could delay emergency treatment for the participant. If a participant's treatment assignment is unblinded, the Sponsor must be notified within 24 hours of this occurrence. The date and reason that the blind was broken must be recorded in the source documentation and database (e-CRF), as applicable.

The code breaks for the study will be held in the Early RA 3TR database back-end with the Data Safe Heaven (ITS) as back-up and are the responsibility of EMR IT Systems and Project Manager. In the event a code break is required, the Investigator or responsible delegate will use the code break to confirm the participant's treatment allocation and relay this information to the required individuals. If the person requiring the unblinding is not associated with the study team, that health care professional will notify the Investigator team that an unblinding is required for a study participant.
In the Early RA 3TR database a 24/7 unblinded procedure will be in place with a code breaks page accessible only to the Investigator or responsible delegate such as the Co-investigator. To unblind the participant:

1. Investigator or responsible delegate will be required to access the database accessible 24/7
2. Open the patient page and click on the “Unblind” tab
3. Request to unblind the patient, add the reason and their password to verify their request.
4. The Early RA 3TR database will unblind the treatment allocation and show it on the patient record.
5. An automatic email will be generated by the Database and sent to the local site contacts and the Chief Investigator and clinical team at QMUL.

The PI or delegate will notify the CI in writing as soon as possible following the code break detailing the necessity of the code break.

In case of patient presents to A&E, the patient will be advised to bring with them the Patient Diary Card for the duration of the study. On the card will be reported the “Rheumatology Study Team Telephone” in case the patient needs to be unblinded for an emergency. Following the contact with the local Rheumatology Study Team, the PI or delegate will log in to the database, as detailed above, and unblind the patient as requested by the A&E doctors.

In case the patient does not have the card with them and therefore contacting the local Rheumatology Study Team will be impossible, they will be treated as if on active arm (Abatacept).

7.5 Study assessments

All trial activities and the visits at which they should be undertaken are documented in the “Schedule of Assessments” table.

7.5.1 Screening procedures (visit 1)

During the screening visit, written informed consent will be obtained from all patients by the Principal investigator or his/her designee before any protocol-specific procedure is performed. Study details, risks and benefits will all be reviewed and patients will be encouraged to ask questions and clarify any concerns. Demographic data (including age, assigned sex at birth and race) and medical history will be obtained. Patients, both men and women, will be reminded to use an acceptable and effective method of contraception during the study period and the appropriate time period after stopping study treatment. Patients may be screened up to 6 weeks prior to baseline visit. As per the study visit schedule screening will entail evaluation of:

- Inclusion and exclusion criteria
- Demographic data including age, assigned sex at birth, and race
- 2010 ACR/EULAR RA classification criteria
- Systemic disease assessment (RA involvement)
- Medical history
- Procedures history
- Allergies
- Concomitant medication
- DMARD therapy
- Corticosteroid therapy
- Clinical examination
- Rheumatoid Factor (RF) and Anti-CCP antibodies (CCP)[a]
- Routine blood tests (ESR, CRP, Full blood count (Haemoglobin, Red Cell Count,

- Haematocrit, White Blood Counts + differential – including lymphocytes and
- neutrophils, Platelet count) liver function tests (ALT, AST), Kidney function/U&E (urea, sodium, potassium, creatinine, eGFR)[b]
- Total cholesterol, HDL, LDL, and triglycerides
- Hepatitis serology, HIV and IGRA[c]
- Vital signs
- Chest X-ray[d]
- ECG
- Pregnancy test[e]
- Joint assessment
- ACR-core set measures
- DAS 28 assessment
- Clinical Disease Activity Index (CDAI)
- VAS Pain score
- US assessment[f]

Note: Anti-TNF therapy screening to include TB screening (IGRA), screening for Hepatitis and HIV according to local guidelines.

[a] RF/CCP tests should be performed unless these tests have been done previously and do not need repeating as per local guidelines.
[b] Routine blood tests do not need to be taken if the patient has already had these performed within 3 weeks of the screening visit
[c] Hepatitis B screening must be performed unless it has been done in the preceding 3 months of the screening visit. If core antibody result is positive but the surface antigen and the viral load result is negative it is assessed as indicating a 'negative' overall result and therefore result is deemed as negative. TB (IGRA), Hepatitis C, and HIV screening is not mandatory; however, all centres are expected to act according to local guidelines with respect to patient screening prior to Anti-TNF and sarilumab therapy.
[d]A chest x-ray must be performed as screening for tuberculosis prior to biological therapy. A chest x-ray must be done at the screening visit to confirm the patient's eligibility, unless a chest X-Ray has been done in the preceding 3 months of the screening visit and the patient must not have had any pulmonary symptoms since then.
[e]A pregnancy test will be performed at each study visit for female patients of childbearing age irrespective of the use of contraceptive methods.
[f]US assessment will be of the joint selected for biopsy to ensure that there is sufficient thickening to meet the following inclusion criterion: selected joint for biopsy must be minimum grade 2 synovial thickening, as assessed at the biopsy visit. This scan will not be reviewed centrally and is optional and not required if the site is confident that the joint will show sufficient inflammation at the biopsy visit.

Note: examples of reliable forms of contraception during the trial are: oral contraceptive and condom, intra-uterine device (IUD) and condom, diaphragm with spermicide and condom. Patients should continue to use a reliable form of contraception for 3 months after their last treatment if on sarilumab, or 3 weeks after their last treatment if they are on etanercept. Males with a partner of childbearing potential, will also be asked to use contraception for the duration of the study.

Note: a woman is considered of childbearing potential (WOCBP) i.e. fertile, following menarche (first occurrence of menstruation) and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

Note: a postmenopausal state is defined as no menstruation for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, a single FSH measurement is insufficient if the patient has not stopped menstruating for 12 months.

7.5.2 Biopsy visit and randomisation (visit 2)

All Patients in the main study will receive a synovial biopsy (refer to 3TR Synovial Biopsy SOP) between 1 to 3 weeks prior to their baseline visit. Patients will have the following assessments recorded prior to the synovial biopsy at this visit:

- Concomitant medication
- DMARD therapy
- Corticosteroid therapy
- Routine blood tests (ESR, CRP, Full blood count (Haemoglobin, Red Cell Count, Haematocrit, White Blood Counts + differential – including lymphocytes and neutrophils, Platelet count) liver function tests (ALT, AST), Kidney function/U&E (urea, sodium, potassium, creatinine, eGFR)[a]
- Study specific bloods
- Vital signs
- Pregnancy test in female patients of child bearing potential [b]
- Joint assessment [c]
- DAS 28
- CDAI
- ACR-core set measures
- VAS Pain Score
- Pre Biopsy Assessment Form
- Adverse events
- Ultrasound examination of the patients' joints prior to the synovial biopsy
- Pre-baseline synovial biopsy [d]
- Randomisation[e]

[a] Routine blood tests do not need to be taken if the patient has already had routine blood tests performed within 3 weeks of the biopsy visit.
[b] A pregnancy test will be performed at each study visit for female patients of child-bearing age irrespective of the use of contraceptive methods
[c] Joint assessments and VAS physician assessment are only required to be completed by the blinded joint assessor from the baseline visit onwards. If possible, the same assessor should perform the joint count at all (pre- and post-randomisation) visits from baseline to ensure consistency.
[d] A synovial biopsy prior to baseline is mandatory for patients in the main study as part of the patient stratification process.
[e] Randomisation see section 7.4

7.5.3 Biopsy visit and randomisation (visit 3)

Patients will receive Abatacept or placebo at their baseline visit depending upon randomisation and/or the treatment allocation algorithm. All assessments should be performed prior to the commencement of therapy. Patients at baseline will have the following assessments:

- Concomitant Medication
- DMARD therapy
- Corticosteroid therapy

- Clinical examination
- Cardiovascular risk assessment
- Routine blood tests (ESR, CRP, Full blood count (Haemoglobin, Red Cell Count, Haematocrit, White Blood Counts + differential – including lymphocytes and neutrophils, Platelet count) liver function tests (ALT, AST), Kidney function/U&E (urea, sodium, potassium, creatinine, eGFR)
- Vital signs
- Pregnancy test in women of childbearing potential [a]
- Joint assessment
- ACR core set measures
- Disease activity core data set (DAS28)
- Clinical Disease Activity Index (CDAI)
- VAS Pain score
- Physical function using the Health Assessment Questionnaire (HAQ)
- SF-36v2© (Licenced by Quality Metric Incorporated)
- FACIT - Fatigue Questionnaire
- EQ-5D-5L
- Post Biopsy Assessment Form
- Adverse events
- Plain X-rays of hands and feet [b]
- Ultrasound assessment
- Optional urine, stool and saliva samples

All baseline assessments should be done within a +/- 7 day window

[a] A pregnancy test will be performed at each study visit for female patients of child bearing age irrespective of the use of contraceptive methods
[b] Plain X-rays of hands and feet do not need to be redone if the patient has already had them within 8 weeks of the baseline visit.

7.5.4 Follow-up (visits 4-7)

Patients will be monitored on a 4-weekly basis as shown in the study visit schedule (Table 1), Section 8.2). Patients will be followed up to 16 weeks. If the study is running at the particular site, there is a potential for patients to be recruited into a long term follow up study: CReMSIA (REC ref: 17/EE/0119). Data collection in the CReMSIA study will be recorded in an electronic CRF. Patients will be followed up as per best practice as currently done in the academic centre participating in the trial.

Safety blood tests will be undertaken every 4 weeks. Additional blood tests for monitoring of toxicity/safety of therapy may be undertaken at the physician's discretion. The ACR 50, a validated composite end point, will be used to assess response to therapy as the primary outcome measure. The Health Assessment Questionnaire, EQ-5D-5L and SF-36 will be used to gauge functional ability and improvement in other aspects of the patients' life. The ESS will be used to measure a patient's sleepiness.

Visits 4 - 7 will be carried out every 4 weeks (±7 days) from the baseline visit. The Principal Investigator will need to review any non-compliance with a view to withdrawing patients at their discretion if drug schedule is adversely affected. Patients who consent to the biopsy procedure at Visit 7 (Week 16) will be asked to complete the Pre Biopsy Assessment Form at Visit 7 (week 16) and the Post Biopsy Assessment Form at the safety follow up visit. If the safety

follow-up visit is completed over the phone, this questionnaire will be completed over the phone.

As per normal clinical practice, the GPs of participants with active RA and a cardiovascular risk profile will be informed and asked to review treatment.

All joint assessments from baseline will be performed by a member of the local trial team who will be blinded to treatment allocation. The joint assessor should also complete the VAS physician assessment component of the VAS Pain Score questionnaire. Data will be entered in the electronic CRF by the Investigator or designee who will also coordinate data validation checks and query resolution.

Patients will be asked to complete a patient diary to log when they have taken their medication. The research team should ask patients to return their empty pens in the packaging used to dispense them at each visit. This will be reconciled by the research team against the patient diary and subsequently destroyed by the research team.

7.5.5 Unscheduled visits

While patients will be encouraged to attend for the normal visit schedule, unscheduled visits will be undertaken if the patient is unwell or there are any concerns as to the patient's progress.

7.5.6 Therapy – Methotrexate

All patients will receive oral methotrexate therapy for the duration of the trial in combination with randomised treatment (blinded abatacept or placebo). Patients will be treated with methotrexate as per best practice in line with EULAR recommendations for rheumatoid arthritis. Starting dose should be 15mg per week. This should be escalated to a weekly dose of about 0.3 mg/kg and that this escalation should be done within 4–6 weeks. Optimal therapeutic dose will be around 20–25 mg per week and should be achieved within 4-6 weeks.

7.6 Study Clinical Outcome measures

Patients will be assessed for disease activity using clinical assessments at baseline and 4 weekly thereafter. All patients will be asked to complete a series of case report forms at baseline and during follow-up as per the 3TR-PARTNER-RA Visit Schedule. Patients will be assessed clinically using the ACR 20/50/70, CDAI (Clinical disease activity index), DAS 28, Health assessment questionnaire, the Short Form 36, FACIT-fatigue questionnaire, EQ-5D-5L and the Epworth Sleepiness scale as described below.

7.6.1 ACR Criteria

The 2010 ACR/EULAR Rheumatoid Arthritis classification criteria will be assessed at screening. Patients are scored out of a maximum of 10, based upon the following elements:

1. **Joint involvement**
2. **Serology** – positivity of rheumatoid factor (RF) and/or anti-citrullinated protein antibody (ACPA)
3. **Acute phase reactants** – erythrocyte sedimentation rate (ESR) and/or c-reactive protein (CRP)

4. **Symptom duration**

7.6.2 Diagnosis and Prognosis Evaluation

Following the diagnostic assessments at the screening visits, patients will be diagnosed with Rheumatoid arthritis.

7.6.3 Joint Assessments

The joint assessments will be performed by the delegated blinded joint assessor. The 66/68 joint count which evaluates 66 joints for swelling and 68 joints for tenderness and pain on motion. The hip joints can be assessed for tenderness, but not for swelling. The following joints are included, upper: temporomandibular, sternoclavicular, acromioclavicular, shoulder, elbow, wrist, metacarpophalangeal (MCP), proximal interphalangeal (PIP), and distal interphalangeal; and lower: hip, knee, ankle, tarsus, metatarsophalangeal (MTP), and interphalangeal (IP) joints of the feet.

The 28 joint count will be utilised in order to calculate the DAS28 score, assessing 28 joints for swelling and tenderness in response to pressure or passive motion. The following 28 joints are included: finger proximal interphalangeal joints (8), thumb interphalangeal joint (2), metacarpophalangeal (MCP) (10), wrists (2) (includes carpometacarpal, intercarpal, and radiocarpal), elbows (2), shoulders (2), and knees (2).

Joint pain with palpation or pain on passive motion (either is sufficient) will be scored as:
0 = No pain
1 = Pain

Joint swelling will be scored as:
0 = No swelling
1 = Swelling

Any joints unable to be assessed should be documented.

7.6.4 Disease Activity Score (DAS28) and Clinical Disease Activity Index (CDAI)

The components of the DAS28 are the number of tender joints (28 joint count, **TEN28**), the number of swollen joints (28 joint count, **SW28**), the Patient Global Health Index Score (100 mm VAS, **GH**), and the CRP (in mg/L) for DAS28 (CRP) or ESR (in mm/hr) for DAS28 (ESR).

The formulae for determining the DAS28 are as follows:

$$DAS28\ (CRP) = 0.56*\sqrt{(TJC28)} + 0.28*\sqrt{(SJC28)} + 0.36*\ln(CRP+1) + 0.014*GH\ (VAS) + 0.96$$

$$DAS28\ (ESR) = 0.56*\sqrt{(TJC28)} + 0.28*\sqrt{(SJC28)} + 0.7*\ln(ESR) + 0.014*GH$$

DAS28 values >5.1 correspond to a high disease activity; values between 3.2 and 5.1 indicate moderate disease activity; values between 2.6 and 3.2 define low disease activity, and values < 2.6 represent remission.

Clinical response will be assessed according to the EULAR response criteria as summarised by the table below.

		DAS28 Improvement		
		> 1.2	**> 0.6 and ≤ 1.2**	**≤ 0.6**
	≤ 3.2	Good response	Moderate response	No response

Present DAS28	**> 3.2 and ≤ 5.1**	Moderate response	Moderate response	No response
	> 5.1	Moderate response	No response	No response

The components of the CDAI (Clinical disease activity Index) are tender joints (28-joint count), the number of swollen joints (28-joint count), a Patient global health index (10 cm VAS) and physician global health index (10 cm VAS). This provides an assessment of RA disease activity on a scale from 0-76.

CDAI scores:
- High disease activity: >22
- Moderate disease activity: 10 < CDAI ≤ 22
- Low disease activity 2.8 < CDAI ≤ 10
- Remission ≤ 2.8

7.6.5 Visual Analogue Scoring – VAS

Participants will be asked to complete three visual analogue scores (VAS), with questions relating to tiredness levels, pain levels, and a patient global health index. The blinded joint assessor will complete the physician global health index score. All VAS scales should be completed by transecting the line, on a 100-mm scale. The scores will be measured in mm.

The pain scale is designed to obtain data relative to the presence or absence of arthritis-related pain and its severity. The objective is to obtain information from patients on how their pain is on the day of the visit, even though pain may be reported to vary over the course of a day or from day to day.

7.6.6 Health Assessment Questionnaire (HAQ) - Disability Index

The Health Assessment Questionnaire (HAQ) is widely used throughout the world and has become a mandated outcome measure for clinical trials in rheumatoid. The Disability Index is sensitive to change and is a good predictor of future disability and costs.

The HAQ is usually self-administered but can also be given face-to-face in a clinical setting. The Disability Index consists of eight categories assessed by the Disability Index are 1) dressing and grooming, 2) arising, 3) eating, 4) walking, 5) hygiene, 6) reach, 7) grip, and 8) common daily activities. For each of these categories, patients report the amount of difficulty they have in performing two or three specific activities. Patients usually find the HAQ Disability Index entirely self-explanatory.

7.6.7 The Short Form (36) Health Survey- SF-36

The Short Form (36) Health Survey is a survey of patient health. The SF-36 is a measure of health status and is commonly used in health economics as a variable in the quality-adjusted life year calculation to determine the cost-effectiveness of a health treatment. The SF-36 consists of eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight.

The eight sections are: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health.

7.6.8 FACIT-fatigue

The FACIT-Fatigue scale is a 13-item, symptom-specific subscale of the FACIT scales. Lower values of the FACIT-Fatigue score denote higher fatigue (score range, 0 to 52). Cella et. al. validated a brief measure of fatigue in rheumatoid arthritis (RA), the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale. The FACIT Fatigue was tested along with measures previously validated in RA: the Multidimensional Assessment of Fatigue (MAF) and Medical Outcomes Study Short-Form 36 (SF-36) Vitality. The FACIT Fatigue showed good internal consistency (alpha = 0.86 to 0.87), strong association with SF-36 Vitality (r = 0.73 to 0.84) and MAF (r = -0.84 to -0.88), and the ability to differentiate patients according to clinical change using the American College of Rheumatology (ACR) response criteria (ACR 20/50/70). This suggests that the FACIT Fatigue is a brief, valid measure for monitoring this important symptom and its effects on patients with RA.

7.6.9 Epworth Sleepiness Scale (ESS)

The Epworth Sleepiness Scale (ESS) is a questionnaire developed to assess “daytime sleepiness.” The questionnaire consists of 8 questions. Respondents are asked to rate, on a 4-point scale (0-3), their usual chances of dozing off or falling asleep while engaged in eight different activities. The ESS score (the sim of 8 item scores, 0-3) can range from 0-24. The higher the ESS score, the higher that person’s average sleep propensity in daily life (ASP), or their ‘daytime sleepiness.

7.6.10 EQ-5D-5L

The EQ-5D-5L consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).

The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient’s health state.

The EQ VAS records the patient’s self-rated health on a vertical visual analogue scale, where the endpoints are labelled ‘The best health you can imagine’ and ‘The worst health you can imagine’. The VAS can be used as a quantitative measure of health outcomes that reflect the patient’s own judgement.

7.6.11 ACR20/50/70

ACR response will utilise 66/68 joint count which evaluates 66 joints for swelling and 68 joints for tenderness and pain on motion. The hip joints can be assessed for tenderness, but not for swelling. The following joints are included, upper: temporomandibular, sternoclavicular, acromioclavicular, shoulder, elbow, wrist, metacarpophalangeal (MCP), proximalinterphalangeal (PIP), and distal interphalangeal; and lower: hip, knee, ankle, tarsus, metatarsophalangeal (MTP), and interphalangeal (IP) joints of the feet.

ACR20/50/70 response can be used to identify responders/non-responders. The following definition of a responder is used for ACR50: ≥50% improvement in tender and swollen joint counts and ≥50% improvement in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments (both 10 cm VAS), pain (VAS), disability as measured by HAQ,

and an acute-phase reactant. The same definition is used for ACR20 and ACR70 using ≥20% and ≥70% improvements respectively.

The ACR20/50/70 will be calculated by the statistician as part of the exploratory analyses.

7.6.12 Pre & Post Biopsy Questionnaire

Prior to and following the biopsy procedure, patients & clinicians will complete pre and post biopsy questionnaires. The pre and post-biopsy questionnaires are developed by EMR to collect information on the safety and tolerability of the synovial biopsy procedure. A standard questionnaire will be administered to all patients immediately pre-biopsy and at the subsequent visit post-biopsy. Patients indicate pain, swelling and stiffness of the biopsied joint pre and post procedure using a visual analogue score (VAS). In the post-biopsy questionnaire patients were also asked to record the level of pain or discomfort suffered during the procedure, additional analgesics taken, and specific adverse events of interest are recorded.

Laboratory Evaluations and Study Sample Collection

7.6.13 Local Blood Sampling

Bloods will be taken for local laboratory investigations at each clinic visit as per the study visit schedule. These include ESR, CRP, Haematology (Hb, Haematocrit, WBC, platelet count, neutrophils, lymphocytes, Red blood cell count, Mean cell haemoglobin, Mean cell volume), and Biochemistry (Urea, sodium, Creatinine, potassium, ALT, AST).

7.6.14 Study Blood Sampling

Blood will be collected as per local guidelines by qualified phlebotomist and as per the Schedule of Assessments Table.

As described in the Lab Manual, blood samples will be sent by a reputable licensed courier:

1. immediately to the central laboratory at EMR at room temperature for processing and storage at the EMR Biobank (see lab Manual).
2. blood RNA will be stored on site at -80C and then sent by courier on dry ice to the Andalusian Public Health System Biobank, Centro de Investigación Biomédica, Avda. del Conocimiento s/n, 18016, Granada, Spain

Study specific bloods from Cagliari patients will be processed at 3TR consortium partner: Laboratorio Diagnosi e Cura Malattie Reumatiche Sistemiche, Secondo Piano, Blocco N,Policlinico Duilio Casula AOU Cagliari SS 554 bivio per Sestu 09042, Monserrato, Cagliari. PBMCs, plasma and serum will be processed on-site and frozen at -80C with blood RNA and blood DNA. The samples will then be sent by reputable licensed courier in batches to the Centre for Experimental Medicine and Rheumatology laboratory on dry ice.

7.6.15 Stool, Urine, and Saliva Sampling (optional) (for future analysis- not within the scope of this protocol)

Stool, urine, and saliva samples will be optionally collected as per the Schedule of Assessments and sent to the central laboratories (see section 9.1) part of the 3TR consortium for analyses and storage at the Institute of Clinical Molecular Biology at Kiel University and/or Andalusian Public Health System Biobank, Centro de Investigación Biomédica, Avda. del

Conocimiento s/n, 18016, Granada, Spain) at -80C as described in section 4.5. They will transfer by reputable licensed courier.

7.6.16 Synovial Biopsy

Minimally invasive ultrasound-guided or arthroscopic synovial biopsies are mandatory at visit 2 to collect synovial tissue. Prior to the procedure, synovial fluid will also be collected, when available, and stored (please refer to the Sample Collection and Shipment SOP). Both procedures will be carried out by the local trained experts (see biopsy manual). At baseline, patients will have at least one joint biopsied. The joint/joints selected for synovial biopsy should have a synovial thickening (ST) of grade 2 or above. Tissue samples will be collected as described in the Sample collecting and shipment SOP:

1. Formalin, RNA later at room temperature and ship immediately to EMR central laboratory by reputable licensed courier. Please refer to the lab manual.
2. Cryostone froze at -80Cand ship in dry iced and sent to the EMR central laboratory for analyses by reputable licensed courier. Please refer to the lab manual.

If a participant does not undergo a baseline biopsy for any reason, they will be withdrawn from the study. Additionally, patients who have a biopsy sample with insufficient RNA for Nanostring analysis, they will be withdrawn from further participation in the trial. This should be communicated to the patient by the principal investigator or delegated clinician, and patients will continue to receive treatment as per standard routine care.

Biopsy at week 16

The biopsy at week 16 will be conducted in the same way using the same method as the pre-treatment biopsy, but a different joint may be biopsied after assessment by and at the discretion of the study clinicians if the original joint is deemed unsuitable for biopsy. Patients will be asked to consent or opt out.

Imaging Evaluations

Patients will have plain x-rays and ultrasound assessments of disease activity and joint damage and will be related to the exploratory outcome measures in this study. Arrangements will be made to facilitate the transfer of X-ray images of the hands and feet and US assessments from participating sites to the 3TR-PARTNER-RA Trial Office as detailed in the 3TR-PARTNER-RA Trial Operational Guide SOP.

7.6.17 Ultrasound

An optional full US set will be performed by a trained member of the site team during the baseline and 16-week follow-up. Images will be acquired and centrally scored at the 3TR-PARTNER-RA Trials office for Doppler signal and synovial thickness. The core US data set is described in the “3TR -PARTNER-RA US Manual”. Each joint will receive a score (0-3) for Power Doppler and (0-3) for Synovial thickening. Additional joints may be scanned at the local centre discretion. Details are provided in the 3TR Precis-The-RA Trial US Manual.

Due to variation amongst Rheumatology departments with regards to resources and expertise to perform ultrasound assessments these will be optional for the purpose of this trial. Any opt-outs will be documented as part of the site set-up and initiation procedures for all participating sites.

Please refer to the Ultrasound Manual for full details of US requirements.

7.6.18 X-rays

Digital radiographs of hands, wrists and feet will be taken using standardised views, in line with routine clinical care. X-rays will be scored centrally by the van der Heijde/Sharp scoring system. The images will be recorded at week 0 and 16. Images should be pseudo-anonymised and sent to the central coordinating centre as soon as possible. The central coordinating office will follow up with sites at regular intervals to ensure images are being sent in a timely manner.

A chest x-ray will be acquired as screening for tuberculosis at or prior to the screening visit, as described in the Schedule of Assessments Table.

7.7 End of Trial- standard of care

Treatment target is low disease activity or remission. Clinical response will be assessed after the end of the trial, if there is high or moderate disease activity, only patient randomised to placebo arm may be offered the chance to join the Established Rheumatoid Arthritis branch of the 3TR study (3TR Precis-The-RA) provided they meet the inclusion criteria. Otherwise, the patient will leave the 3TR study and continue to be managed according to their local guidelines.

At the end of the trial, when the treatment is unblinded, if a patient randomised to the placebo arm of 3TR-PARTNER-RA study consents to undergo the week 16 biopsy, they will be eligible for 3TR's established RA trial (3TR Precis-The-RA Study) and will be screened for inclusion.

Instead, if the patient randomised to the placebo arm of 3TR-PARTNER-RA study opts out of having a second biopsy at week 16, they will be eligible to participate in the 3TR Precis-The-RA Sub-study which does not require a repeat biopsy.

Only patients randomised to the placebo arm of the 3TR-PARTNER-RA study could be eligible for the 3TR Precis-The-RA study or 3TR Precis-The-RA Sub-study due to the exclusion criteria: no prior exposure to any biologic/targeted DMARDs for RA.

Patients who do not join the Established Rheumatoid Arthritis branch of the 3TR study (3TR Precis-The-RA) will be given the opportunity to be followed up as part of the longitudinal observational research database, CReMSIA research database (if open at the research site) whereby patients consent for their clinical information obtained at routine NHS visits to be recorded on a database.

If a patient ceases the trial intervention during their participation in this study, this information including the reason should be recorded via the treatment cessation/withdrawal page in the Early RA 3TR Database. The patient can continue to attend study visits unless the patient has withdrawn consent from attending any further study visits.

Participants will not have access to the study intervention after the end of their participation and may return to the standard of care received prior to entering the study, at the discretion of their physician. At the end of week 16, the treatment allocation will be unblinded to allow the physician and the participant to decide the standard of care. This will generate an email sent also to the QMUL clinical trial team. The principal investigator will report the treatment allocation on the e-CRF.

7.8 Follow up procedures

Only completion of the trial intervention at 16 weeks, patients will be contacted 30 days later in order to record any AEs or SAE's that may have occurred during this period. Patients who underwent the additional biopsy at week 16 will also be asked to complete the post-biopsy questionnaire.

8.0 Participant, Study, and Site discontinuation

8.1 Subject Withdrawal from Study/Withdrawal of Consent

Patients who consent to the study but do not undergo synovial biopsy at visit 2 will be withdrawn from the study. Additionally, patients who have a biopsy sample with insufficient RNA for Nanostring analysis will be withdrawn from further participation in the trial. This should be communicated to the patient by the principal investigator or delegated clinician, and patients will receive treatment as per routine care.

Participants may cease randomised treatment and/or be withdrawn from the study if they no longer fulfil the participation criteria, at physician's discretion. Subjects may also withdraw consent for any reason at any time without prejudice to their normal care or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. Samples collected prior to withdrawal will be kept unless the patient specifically requests otherwise. The PIS will make clear to participants that data collected prior to withdrawal will be kept and their rights to destroy this data are limited.

8.2 Withdrawal procedure

At the time of withdrawal, the withdrawal CRF should be completed. The reason for discontinuation should be documented on the applicable CRF and medical records. Patients who discontinue their randomised treatment should be asked to attend the week 16 visit (visit 7) in order to collect data for the primary analysis. However, if the patient discontinues randomised treatment and withdraws consent from attending any further visits, no further study visits should be carried out.
If the patient does not undergo the baseline synovial biopsy, the withdrawal CRF should be completed, and no further study visits should be carried out.

9.0 Laboratories and samples

For full details regarding tissue and blood collection, transport, and analyses, please refer to the study Lab manual.

9.1 Central laboratories

Synovial tissue and study blood analyses will be performed at:

Centre for Experimental Medicine and Rheumatology,
2nd Floor, John Vane Science Centre
William Harvey Research Institute
Barts and the London School of Medicine and Dentistry
Charterhouse Square
London EC1M 6BQ.

Tissue samples will also be stored at EMR Biobank (site license 12199) at Queen Mary University under the Human Tissue Act 2014 for future use and long-term storage.

Stool, urine and saliva sample analysis (for future analysis- not within the scope of this protocol)

Stool sample analysis will be performed at Systems Immunology, Institute of Clinical Molecular Biology, Kiel University (CAU), Am Botanischen Garten 11, 24118 Kiel, Germany and/or Andalusian Public Health System Biobank, Centro de Investigación Biomédica, Avda. del Conocimiento s/n, 18016, Granada, Spain.

Blood (RNA and DNA), urine and saliva sample analysis will be performed at the Andalusian Public Health System Biobank, Centro de Investigación Biomédica, Avda. del Conocimiento s/n, 18016, Granada, Spain.

Stool, saliva and urine samples will be transported by an approved courier company.

9.2 Local laboratories

Bloods (RF & CCP, haematology, biochemistry panel, ESR, CRP, Hepatitis serology, HIV, IGRA, as described in the Schedule of Assessments Table) will be analysed at the patient's local hospital, as per local guidelines.

9.3 Sample collection, labelling, and logging

Details on the process of sample collection/labelling and logging from the patient, as well as pseudo-anonymisation prior to expedition to the laboratories are provided in the Trial Sample Collection and Shipment SOP.

9.4 Sample transfer, chain of custody, and accountability

Details of sample receipt, chain of custody, and accountability are contained in the Trial Sample Collection and Shipment SOP. Sample logs will be maintained at Sites and Laboratories.

9.5 Sample analysis procedures

9.5.1 Peripheral blood analysis

Local site laboratory - The following blood tests will be performed as per the Schedule of Assessments Table. (ESR, CRP, Full blood count (Haemoglobin, Red Cell Count, Haematocrit, White Blood Counts + differential – including lymphocytes and neutrophils, Platelet count) liver function tests (ALT, AST), Kidney function/U&E (urea, sodium, potassium, creatinine, eGFR). These bloods may be repeated as required if the sample is unable to be processed at the local laboratory. These investigations will be performed at the local site laboratory. RF and CCP will be performed at screening, if not already performed and documented in the patients' medical records.

QMUL, Experimental Medicine and Rheumatology - Study specific bloods will be taken as mentioned in the lab manual. No more than 40ml of blood should be taken from the patient on on biopsy visit (visit 2) and follow-up visit (visit 7) for the isolation of plasma, PBMCs, serum, blood RNA and blood DNA. For visit 4,5 and 6, 20ml of blood should be taken for the isolation of plasma, PBMCs and serum.

Further details of sample requirements, handling, transfer and storage are contained in the trials Sample Collection and Shipment SOP.

9.5.2 Synovial biopsies and tissue analysis

Synovial biopsies (either US-guided or arthroscopic) will be performed at baseline and 16 weeks. The biopsy prior to baseline is mandatory, while the biopsy at week 16 is additional and not mandatory.

Synovial fluid -whenever available- will also be collected and stored concurrently with each biopsy. Tissue will be:

1. Immersed in RNA-Later® for RNA extraction
2. Processed for paraffin embedding for histological analysis
3. Frozen for single cell analysis.

Further details of sample requirements, handling, transfer and storage are contained in the Lab Manual.

Molecular Analysis

Participants will be defined according to Nanostring panels as described in the Molecular Analysis SOP.

Nanostring have developed specific gene expression panels based on the revision of RNA-Seq based gene list using Nanostring in-house algorithms, including checks on gene suitability and quality control, followed by manufacture and transfer of the Nanostring probes into a commercial grade Nanostring panel. This Nanostring panel will be validated on synovial tissue RNA from selected RA patients from the PEAC, STRAP and R4RA cohorts.

RNA extraction

QMUL, Experimental Medicine and Rheumatology – Biopsies preserved in RNA-Later® will be processed to extract RNA/DNA and protein according to the Sample Processing SOP. The resulting components will be quantified, and quality checked according to the same SOP.

NCounter assay

QMUL, Experimental Medicine and Rheumatology - RNA samples, which have passed the QC will be assayed using the 3TR panel from NanoString (list of probes specified in the SOP) using nCounter Sprint machine as described in the Molecular Analysis SOP.

Future analysis

Biospecimens (whole blood for serum, plasma, peripheral blood mononuclear cells, RNA, and DNA, biopsy and stool samples) will be collected at specified time points in the study schedule throughout the study to evaluate known and/or novel disease-related or drug-related biomarkers in circulation or at tissue sites.

Types of biomarkers may include nucleic acids, proteins, cell populations, lipids, and/or metabolites, either free or in association with particular cell types. The analyses may include but are not limited to soluble proteins, genomic transcripts, blood leukocyte populations, and genetic analysis.

Results from this optional biomarker research will not be included in the clinical study report.

9.6 Sample Storage Procedures

Samples will be transported to the central laboratory by an approved courier company. Samples or fractions thereof not used immediately for experimental analyses may be stored in the EMR Biobank (site license 12199) at Queen Mary University under the Human Tissue Act 2014 for future use. This will allow for further research analyses in the future, guided by scientific advancements in the field. The sponsor will ensure that the samples are kept securely and handled in line with the consent given by the patient.

9.7 Sample and result recording and reporting

Sample collection will be documented on a hard copy log sheet and sent to the central laboratory with the samples. Sample receipt and the results of analyses will be entered into the web-based database according to the Sample Data Entry SOP. The sample section of the database will be separate from the eCRF and will be accessible to delegated central laboratory and coordinating staff only. Molecular Analysis raw data will be recorded in 2 secure locations.

9.8 Sample Management at End of study

Samples collected during this project will be stored in a licensed research tissue bank at the end of the project and will be used in future research as described in section 9.6. Participants will be asked to give informed consent for their samples to be stored in a tissue bank for use in future research.

10.0 Study medication

Please also refer to the IMP Manual.

10.1 Name and description of Investigational Medicinal Product(s) (IMP)

Abatacept
Subcutaneous
Abatacept is a fusion protein produced by recombinant DNA technology in Chinese hamster ovary cells. Abatacept (ORENCIA 125 mg solution for injection in a pre-filled syringe) is available in a pre-filled syringe containing 125 mg of abatacept in one mL and administered subcutaneously. The solution is clear, colourless to pale yellow with a pH of 6.8 to 7.4. Placebo for abatacept injection for SC administration is a sterile solution product that compositionally matches the active product except for the absence of abatacept.
Abatacept and placebo will be provided by the manufacturer, BMS.

11.0 Legal status of IMP

Abatacept (ORENCIA) is licensed for the treatment of RA and is authorised for use in the UK and EU.

The trial will be carried out under a Clinical Trial Authorisation (CTA). The drug is therefore only to be used by the named investigators, for the participants specified in this protocol, and within the trial.

11.1 Name and description of each Non-Investigational Medicinal Product (NIMP)

Methotrexate

All patients will receive oral methotrexate therapy for the duration of the trial in combination with randomised treatment (blinded abatacept or placebo). Methotrexate will be sourced from local hospital stocks and prescribed as per local guidelines. Patients will be treated with methotrexate as per best practice in line with EULAR recommendations for rheumatoid arthritis. Starting dose should be 15mg per week. This should be escalated to a weekly dose of about 0.3 mg/kg and that this escalation should be done within 4–6 weeks. Optimal therapeutic dose will be around 20–25 mg per week and should be achieved within 4-6 weeks.

11.2 Legal Status of NIMP

Methotrexate is licensed for the treatment of RA and will be prescribed from local hospital stocks as per local guidelines and in line with EULAR recommendations as described above.

11.3 IMP Manufacturer(s) and supply arrangements

The IMP (abatacept and placebo) will be manufactured by BMS and the supply will be arranged by Modepharma. All IMPs are manufactured according to current GMP and QP released in the UK and EU for clinical trial use. No study drug will be shipped to a site until the site has received greenlight after Site Initiation Visit performed until written Institutional Review Board (IRB)/Ethics Committee (EC) authorization has been received by the Sponsor or its representative.

11.4 Packaging and labelling of IMP(s) and placebo(s)

Abatacept and its matching placebo will be packaged and labelled in a blinded manner for the double blinded treatment manner in accordance with applicable national laws.

11.5 Accountability

Drug accountability will be recorded at the trial site. Pharmacy will record the number of packs received, the number of packs dispensed to which participant, batch number, expiry date, and quantity of IMP product returned by the participant. Any unused IMP and/or empty packaging will be returned to pharmacy for accountability. This will be verified by the clinical trial monitor prior to disposal at site. All dispensing episodes for IMP must be recorded on the 3TR-PARTNER-RA Master Accountability Log for in addition to the patient specific dispensing log in the Pharmacy File.

Use of the sites own accountability logs are permitted as long as all relevant information is recorded. Sites will be requested to provide a template of their accountability logs to the 3TR PARTNER-RA Trials Office for approval prior to use.

Methotrexate will be dispensed for hospital stocks and therefore accountability procedures will not apply.

11.6 Assessment of compliance

Patients will be asked to complete a diary to confirm the timely administration of study treatment. Administration of IMP is weekly. In the event that patients deviate from this they are advised on correct action as detailed in the package leaflet. Patients will be issued with a patient diary at the baseline visit. Patients will record the use of trial medication (including methotrexate) in the diary that will be returned at every clinic visit along with any used syringes. Adherence to the prescribed treatment will be checked at every clinic visit. This will serve as a measure of compliance. All doses included missed doses will be recorded on the eCRF.

11.7 Drug storage

The local Principal Investigator is responsible for the control of drugs under investigation at their site. Adequate records for the receipt (e.g. Drug Receipt Record) and disposition (e.g. Drug Dispensing Log) of the study drug will be maintained. Accountability will be assessed by maintaining adequate drug dispensing and return records. This will be delegated to the local site pharmacy. The IMP will be stored by the local pharmacy. Accurate records must be kept for each study drug provided.

All IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff. The IMP should be stored in a refrigerator (2°C - 8°C), and in the original package in order to protect from light.

Temperature deviations arising at trials sites after drug delivery are the responsibility of the trial site to quarantine and reporting requirements are detailed in the 3TR-PARTNER-RA IMP Manual.

11.8 Prescription and Dispensing of IMP(s), placebo(s), and NIMP(s)

IMP will be prescribed by a clinician who is a member of the study team, using trial specific prescription forms (either Sponsor or local template may be used). Prescription forms should be stored in the trial Pharmacy File and must be available for review for the purposes of monitoring visits/audit inspections throughout the study duration.

A Drug Dispensing Log at Pharmacy will be kept current and will contain the following information:

- Pharmacy dispensed medication (pack #)
- The identification of the patient to whom the study medication was dispensed
- The date[s], quantity of the study medication dispensed to the patient.
- The date[s] and quantity of the study medication returned by the patient.

All records and drug supplies must be available for the purpose of monitoring visits/audit inspections. The trial medication must only be used to treat participants in the 3TR- PARTNER-RA trial.

11.9 Administration of IMP(s), placebo(s), and NIMP(s)

The IMP is intended for use under the guidance of a healthcare professional. After proper training in subcutaneous injection technique, a patient may self-inject the IMP if the nurse or clinician determines that it is appropriate.

After removing the pre-filled syringe from the refrigerator, the pre-filled syringe should be allowed to reach room temperature by waiting 30 minutes, before injecting. The syringe should not be shaken.

The total content (1 mL) of the pre-filled syringe should be administered as a subcutaneous injection only. Injection sites should be rotated, and injections should never be given into areas where the skin is tender, bruised, red, or hard.

11.10 Destruction, return, and recall of IMP(s) and placebo(s)

All IMP that is to be destroyed will be documented and accounted for in accountability/drug destruction logs. This will be delegated to the local site pharmacy. Destruction of the study drug will be as per local requirements and will be authorised by the 3TR-PARTNER-RA Coordinating Office.

The batch number of all IMP supplies will be recorded on the accountability log and recall by IMP suppliers will be managed by the Sponsor.

Disposition of unused study drug not dispensed to patients, or partially used/returned study drug will be recorded as described in the IMP manual. IMP destruction of product not dispensed/administered must be confirmed with and approved by the 3TR-PARTNER-RA trials office.

11.11 Dosage schedules

Abatacept (ORENCIA) should be administered weekly at a dose of 125 mg by subcutaneous (SC) injection.
If a patient misses an injection of Abatacept and is within three days of the planned date, he/she should be instructed to take the missed dose immediately and remain on the original weekly schedule. If the dose is missed by more than three days, the patient should be instructed when to take the next dose based on medical judgment (condition of the patient, status of disease activity, etc).
All doses including missed doses should be documented on the patient diaries and transcribed to the eCRF.

11.12 Dosage modifications and delays

Adherence to the planned dose regimen of study medication is required unless an adjustment is necessary for safety events as per applicable SmPC. All dosage modifications or interruptions should be clearly documented on the eCRFs.

11.13 Management of Abatacept specific adverse events

The clinical team should refer to the relevant current SmPC.

11.14 Known drug reactions and interventions with other therapies

The clinical team should refer to the relevant current SmPC for known drug reactions and interactions.

11.15 Concomitant medications

11.15.1 DMARDs

Patient will not be allowed to take any other conventional, biologic or synthetic DMARDs during the trial.

11.15.2 Non-steroidal anti-inflammatory drugs

The patient will be permitted to be on NSAIDs at any time throughout the duration of the study.

11.15.3 Steroids

Nasal, cream or oral inhaled steroid preparations may be used throughout the study duration. Patients may receive corticosteroids throughout the trial at the discretion of the treating clinician. If steroids are clinically indicated, they should be tapered as rapidly as clinically feasible, in line with EULAR recommendations.

However, within 4 weeks prior to visit 1 (screening), visit 2 (biopsy/baseline), visit 5 (12 weeks), and visit 6 (16 weeks) the corticosteroid dose should not be increased and should not exceed prednisolone 10mg/day (or equivalent).

Intra-articular and other parenteral corticosteroids should not be used in the 4 weeks prior to visit 1 (screening), visit 2 (biopsy/baseline), visit 5 (12 weeks), and visit 6 (16 weeks). Patients may receive corticosteroids (po, intra-articular, or parenteral), if required, at the end of that study visit.

11.15.4 Other medications

Other medications (with the exception of investigational / unlicensed drugs) are permitted as clinically required during the study and should be recorded on the applicable visit Case Report Form (CRF).

11.16 Management of overdose

Any overdoses should be managed as per section 4.9 of the relevant current SmPC.

11.17 Precautions regarding contraception

Abatacept is not recommended for use during pregnancy unless the clinical condition of the woman requires treatment with abatacept. Women of childbearing potential must agree to use effective contraception during treatment and up to 14 weeks after the last dose of abatacept in order to participate in this trial. Pregnant patients will be excluded from this trial and any participant who becomes pregnant during their participation in the trial, will be withdrawn immediately when the study team are notified of pregnancy from trial treatment. Men with partners of childbearing potential will be reminded to use an acceptable and effective method of contraception during the study period and the appropriate time period after stopping study treatment (up to 14 weeks after the last dose of abatacept).

If a participant's partner becomes pregnant whilst or after (up to 14 weeks after the last dose of abatacept) the partner is participating in the trial, pregnant partner will be asked to consent for the clinical team to collect information about their health and their pregnancy. This is optional and if pregnant partner agrees, clinical team will contact them after they have given birth to your baby asking you about their pregnancy and delivery and the health of their baby.

If a participant's partner becomes pregnant whilst the male partner is participating, participant will continue the treatment.

Pregnancy should be reported via a paper form and should be sent to emrclinicaltrials@qmul.ac.uk that will notify and report to the Sponsor (see section 12.9)

11.18 Arrangements for post-study access to IMP and care

Participants will not have access to the study intervention after the end of their participation and may return to the standard of care received prior to entering the study, at the discretion of their usual physician.

12.0 Pharmacovigilance

12.1 General definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "*response to an investigational medicinal product*" means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death. • Is life-threatening. • Requires inpatient hospitalisation or prolongation of existing hospitalisation (excludes day cases) • Results in persistent or significant disability/incapacity. • Consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator or medical assessor, believed with reasonable probability to be due to one of the study treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the Reference Safety Information (RSI): • In the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product. • In the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the study in question.

12.2 Site investigator assessment

The Principal Investigator is responsible for the care of the participant, or in their absence an authorised medic within the research team is responsible for assessment of any event for:

- **Seriousness**

Assessing whether the event is serious according to the definitions given in section 0.

- **Causality**
  Assessing the causality of all serious adverse events/reactions in relation to the study treatment according to the definition given. If the SAE is assessed as having a reasonable causal relationship, then it is defined as a SAR.
- **Expectedness**
  Assessing the expectedness of all SARs according to the definition given. If the SAR is unexpected (as per the RSI), then it is a SUSAR.
- **Severity**
  Assessing the severity of the event according to the following terms and assessments. The intensity of an event should not be confused with the term "serious" which is a regulatory definition based on participant/event endpoint criteria.
    - **Mild**: Some discomfort noted but without disruption of daily life
    - **Moderate**: Discomfort enough to affect/reduce normal activity
    - **Severe**: Complete inability to perform daily activities and lead a normal life

12.3 Reference Safety Information (RSI)

Reference Safety Information (RSI) section 4.8 is the information used for assessing whether an adverse reaction is expected. For this trial, the RSI for abatacept will be the current and most updated version of the Orencia 125 mg solution for injection in pre-filled pen – SmPC.

12.4 Notification and recording of Adverse Events (AEs) or Reactions (ARs)

All AE and AR's are to be documented in the participants' medical notes or other source data documents and the CRF. Once assessed, if the AE is not defined as SERIOUS, the AE is recorded in the eCRF and the participant is followed up by the research team until the AE is considered resolved.

AEs and Serious Adverse Events (SAEs) should be recorded from the time that the first trial specific assessment/procedure is undertaken (screening visit), and then subsequently at follow-up visits throughout duration of trial treatment. Participants should be advised to notify the trial site of any untoward medical events as soon as possible, even if this is outside of their normal visit schedule.

AEs and SAEs should continue to be reported, following the same reporting procedures, throughout the patient's time on the trial and for a further 30+ days after the week 16 visit (or their last dose of IMP, if earlier).

An AE would usually be considered resolved once the main symptoms are no longer present or once the patient is receiving treatment and the event is considered stabilised. If a patient has a new long-term diagnosis made during the trial, this should be documented as recovered with sequalae once the patient is considered stable and the condition is being adequately treated (if applicable), even if the diagnosis is ongoing (for example, if a patient has a new diagnosis such as diabetes during the trial). SAE's resulting in hospitalisation will be considered resolved once the patient is sufficiently recovered enough to be discharged from hospital.

12.4.1 Adverse Events notification to BMS

Non-serious Adverse Events (AE) are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement as part of an annual reporting requirement.

12.5 Adverse events that do not require reporting

The following events are not considered as SAEs for the trial:
- Pregnancy (however it is an event that requires monitoring and follow up- pregnancy CRF must be completed)
- Procedures that were planned prior to the screening visit (although this does not exclude any complications post-procedure)
- Pre-existing conditions prior to the screening visit, unless the condition has worsened

Note: The following definition **is** considered a SAE for this trial:
- Elective surgery at any time, which is related to, or has resulted from, any new or worsening condition.

12.6 Notification and Reporting of Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs)

All Serious Adverse Event (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) will be recorded in the participants' notes, the eCRF, the sponsor SAE form and reported to the sponsor (administered by the Joint Research Management Office or agreed representative) within 24 hours of the site becoming aware of the event.

Nominated co-investigators (as listed in the delegation log for each site) will be authorised to sign the SAE forms in the absence of the PI at the participating sites.

12.6.1 SAEs and SUSARs notification to BMS

All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through *30* days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug**. If applicable,** SAEs must be collected that relate to any follow-up protocol-specified procedure.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours \ 1 Business Day of becoming aware of the event. SAEs must be recorded on either CIOMS, MedWatch, or approved study specifi/institutional SAE form.

If only limited information is initially available, follow-up reports are required.

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours \ 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

12.6.2 Procedures for reporting blinded SUSARs

The CI, as sponsor medical assessor, will assess the event blinded for all possible IMPs, placebos, and combinations.

The Joint Research Management Officer (JRMO) at Queen Mary University of London will be unblinded to facilitate unblind SUSAR reporting to the MHRA. A delegated and trained JRMO will have access by an account with limited access to the Early RA 3TR Database to unblind the participants independently. The IT Systems and Project Manager will report the IMP to Joint Research Management Officer to enable them to report to MHRA in case of issues in accessing the Database from the delegated JRMO.

A delegated member from the clinical team will be responsible for maintaining unblinded records for the trial. This will be recorded in the delegation log for the study.

12.7 Sponsor medical assessment

Sponsor has delegated the responsibility for oversight of IMP safety profile and medical assessment of AEs, ARs, SAEs and SUSARs to the CI as medical assessor The CI must review all SAEs within 72 hours of receipt. This review should encompass seriousness, relatedness, and expectedness. Day 0 for all SUSARs is when the SAE / SUSAR is received by the CI and / or coordinating team and / or sponsor (whichever is first).

It is noted that the CI cannot downgrade the PI assessment of an event's causality. If there is disagreement between CI and PI assessment, no pressure should be placed on the PI to alter their assessment, but the CI can liaise with the site PI before the CI's final decision. The CI and PI assessment can differ.

The CI's assessment will be documented directly on the eCRF.

12.8 Urgent safety measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical study participants from any immediate hazard to their health and safety, in accordance with Regulation 30 of the Medicines for Human Use (Clinical Trials) regulations. The measures should be taken immediately. In this instance, the approval of the Competent Authority prior to implementing these safety measures is not required.

The CI has an obligation to inform both the MHRA and Research Ethics Committee in writing **within 3 days** of implementing the Urgent Safety Measure. They must also submit a substantial amendment documenting the changes with 14 days of implementing the urgent safety measure. The JRMO must be sent a copy of the correspondence with regards to this matter as soon as it is sent.

12.9 Pregnancy

If a participant becomes pregnant whilst involved in a CTIMP, it is not considered to be an SAE or an AE.
However, it is an event that requires reporting, monitoring and follow up. If a participant or participant's partner becomes pregnant whilst or after taking an IMP, the sponsor should be notified immediately (within 24 hours of site becoming aware of the pregnancy) using the

sponsor pregnancy form. The pregnancy reporting procedure will be the same as the SAE reporting route. Pregnancy should be reported via a paper form and should be sent to emrclinicaltrials@qmul.ac.uk

The CI (in conjunction with the site PI) should determine if the foetus has been exposed to an IMP. The PI has the responsibility to ensure that the pregnancy form is completed and sent to the sponsor within the agreed timelines. The initial report should be sent within 24 hours of the PI or co-investigator becoming aware of the event and follow up information submitted as and when it becomes available up to agreed follow up time after birth. For patients receiving abatacept pregnancies will also be reported to the IMP provider (BMS).

The sponsor will arrange for a review of the pregnancy report by an appropriate expert medic (usually a consultant obstetrician). The study team must follow all instructions provided by the sponsor's expert.

In the event of pregnancy, the patient must be withdrawn from the trial interventions and may attend follow ups as per scenario for patients ceasing treatment prior to 16 weeks subject to continued consent.

The PI/CI also must follow up the pregnancy until delivery as well as monitoring the development of the new-born for one month after birth. Any events that occur during this time that could be considered to be a SAE must be reported to the sponsor in line with section 12.7, utilising the SAE CRF reporting form.

12.9.1 Pregnancy notification to BMS

The Sponsor-Investigator must immediately notify BMS of this event and complete one of the following forms **within 24 hours of awareness** of the event via either the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form in accordance with **SAE reporting procedures.**

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the **approved site SAE form**.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor-Investigator or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

13.0 Annual reporting

13.1 Development Safety Update Report (DSUR)

The DSUR will be written by the CI (following Sponsor procedures) and submitted to the sponsor for review prior to submission to the MHRA. The DSUR is due for submission within 60 days of the end of the reporting period. The reporting period is annually from the date on the "*Notice of acceptance letter*" from the MHRA. The sponsor's delegated Medical Assessor, usually the CI, will carry out a risk benefit analysis of the IMPs encompassing all events having arisen on the study. REC will be sent a copy of the DSUR.

The DSUR will be submitted through the CTIS system by the Coordinating Trials office to non-UK Competent Authorities or will be sent to the competent authority by the Lead research team in that country. The lead research team in each country will be responsible for reporting to their ethics committees.

13.2 Annual Progress Report (APR)

Non-UK sites

If required, according to local guidelines, the APR will be written and submitted to the Ethics committee by the Lead Research team of each country. A copy will be provided to the sponsor.

14.0 Statistical and data analysis

14.1 Sample size calculation

The primary analysis of the trial is the comparison between Group 1 and Group 3 (see figure in Section 2.6), i.e. the patients classified as biomarker positive treated with Abatacept + Methotrexate (MTX) (Group 1) vs. the patients classified as biomarker negative treated with Abatacept + Methotrexate (MTX) (Group 3). Since patients will be randomised 1:1 to either Abatacept + MTX or Placebo + MTX and the median value observed in the PEAC study as a cut-off to classify the biomarker status, we expect the comparison groups to be roughly equal. That would allow to ascribe the differences in response we will observe to the different biomarker profiles of the two groups, hence demonstrating if the presence of a biomarker will enhance the response to the any of the drugs included in the trial.
The power calculation is done for this comparison, based on the following assumptions:

- 50% patients will be classified as biomarker positive and 50% as biomarker negative
- Using change in CDAI score from baseline (delta CDAI) as the primary outcome, a difference in delta CDAI between the two comparison groups of 10, with a Standard Deviation of 14.34. These are the values that were observed when analysing the difference in delta CDAI between biomarker positive and biomarker negative patients treated with MTX in the PEAC study. Although PEAC patients were not treated with Abatacept, this comparison is expected to be even more in favour of the biomarker positive group using Abatacept together with MTX. Thus, basing the power calculation on the PEAC observed difference is a conservative assumption.

With these assumptions, 88 patients would be needed to detect a significant difference of 10 in delta CDAI with 90% power (66 patients for 80% power). Since this would only be for Group 1 and Group 3 (44 patients each), a total of 176 patients would be sufficient for 90% power in the whole trial (132 for 80% power) which includes all four groups as per Figure 1 Section 2.6. If we assume a 5% dropout rate and also account for an expected 5% of patients that have insufficient RNA for the Nano-string analysis (based on results from the STRAP trial), 196 patients in the whole trial would be sufficient to detect a significant difference (Group 1 vs Group 3) of 10 in delta CDAI with 90% power (147 patients for 80% power).

14.2 Planned recruitment rate

This study will include at least 10 recruiting centres and recruitment rates at each centre will be reviewed at regular 3TR RA working group meetings. If the recruitment rate is slower than expected, additional centres and PIC sites may be set up in order to meet the recruitment target.

14.3. End of trial (EOT)

The end of the study will be triggered 6 months after the last patient completes their final study visit (Last Patient Last Visit LPLV).

These additional 6 months will allow time for sample processing and image analysis. The end of trial declaration will be submitted within 90 days of the end of trial definition, and this will mark the end of trial data and sample collection, sample and image analysis.

The CI is delegated the responsibility of submitting the EOT notification to REC and MHRA once reviewed by the sponsor. The EOT notification must be received by the REC and MHRA within 90 days of the end of the study. If the study is ended prematurely, the Chief Investigator will notify the Sponsor, REC, and MHRA within 15 days, including the reasons for the premature termination.

For non-UK sites, the reporting of the end of trial to the ethics committee and Competent authority will be delegated to a lead research team in that country. The sponsor (JRMO) must be sent a copy of the correspondence with regards to this matter.

The clinical study report will be submitted within 12 months of the end of trial notification.

14.4 Statistical Analysis

The statistical analysis of the trial will be described in detail in the Statistical Analysis Plan (SAP). This will be finalised prior to the analysis of the data. In brief, the primary outcome, which is a continuous outcome, will be analysed by analysis of covariance (ANCOVA) with treatment as a factor and baseline value as continuous covariate. If assumptions for ANCOVA are not met, non-parametric ANCOVA will be used. Changes from baseline within groups will be analysed with a paired Wilcoxon test. Secondary binary endpoints will be analysed using a χ^2 test unless any element within the contingency table has fewer than 5 individuals in which case a Fisher's exact test will be used.

14.5 Summary of baseline data and flow of participants

Baseline characteristics and clinical data for randomised patients will be summarised but not subjected to statistical testing. All participating sites will be asked to keep a log of consented patients who were screen failures. Reasons for non-participation will be categorised and summarised. Participation in the trial, treatment allocation and completeness of follow-up will be illustrated by a CONSORT flow diagram.

14.6 Analysis of participant populations

For the purposes of the analyses, the following analysis populations are defined.

Randomized population includes all participants who were randomized to the study.

Safety population includes all participants who were randomized and received at least 1 dose of study drug. Safety population will be used for safety analysis. If a participant received study drug dose different from the one to which the participant was randomized, the participant's safety data will be analysed as treated.

Intention-to-treat (ITT) population includes all participants who were randomized and received at least 1 dose of study drug during the Induction Period. ITT population will be used for efficacy analysis. If a participant received a study drug dose different from the one to which the participant was randomized, the participant's efficacy analyses will be performed as randomized.

ITT-Maintenance population includes all participants who were randomized and received at least 1 dose of study drug in Maintenance Period. If a participant received study drug dose different from the one to which the participant was randomized, the participant's efficacy data will be analysed as randomized.

Pharmacokinetic (PK) population includes all participants who were randomized, received at least 1 dose, and have any evaluable plasma concentration of study drug.

Biomarker population includes all participants who were randomised, received at least 1 dose of study drug, and have any evaluable measurement of biomarker of interest.

14.7 Primary endpoint analysis

The primary analysis is within the abatacept arm. It will assess the difference in the change in Clinical Disease Activity Index (CDAI) score at 16 weeks between the biomarker positive and the biomarker negative patients (i.e. Group 1 vs Group 3). This analysis will be on an ITT basis according to original randomisation allocation. The primary outcome will be analysed by analysis of covariance (ANCOVA) with treatment as a factor and baseline value as continuous covariate. If assumptions for ANCOVA are not met, non-parametric ANCOVA will be used. The treatment effect will be reported as least squares mean with 95% confidence intervals.

14.8 Secondary endpoint analysis

The primary analysis will be repeated using the secondary endpoints.

The primary and secondary endpoints will also be used to perform analyses comparing the difference in response between the abatacept and placebo groups with the biomarker positive group against the difference in response between the abatacept and placebo groups with the biomarker negative group.

14.9 Safety analysis

The safety analysis set consists of patients who received at least one dose of the trial medication. Safety analysis will be based on the safety analysis set. All AEs will be recorded, notified, assessed for seriousness, and severity, reported, analysed and managed in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004. The reporting and notification of serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) is specified in the protocol and these events will be summarised by treatment and pathotype.

14.10 Subgroup analyses

Response in individual treatment groups, both overall and by arm, will be presented descriptively.

14.11 Adjusted analysis

Baseline factors will be tested for imbalance between groups. As part of additional exploratory analyses, any imbalanced baseline factors will be considered as covariates in statistical models to determine the effect, if any, of adjusting models with these factors, if this is deemed clinically or biologically appropriate, to determine the robustness of the primary analysis.

14.12 Interim analysis and criteria for the premature termination of the study

There are no planned interim analyses, unless specifically requested by the **Trial Steering Committe**e and these would be reported in a confidential closed session.

14.13 Procedure(s) to account for missing or spurious data

Data cleaning will be performed as documented in the trial Data Management Plan. The Early RA 3TR Database has in-built data checks and validations to ensure a complete and accurate dataset, supplied by Webclinica. These data checks and validations will generate an auto-query if a field is left blank (in most cases the user will be unable to save the page unless the field is completed or indicated as not done) or a value is outside the expect range. The trial coordinating office can generate manual queries as needed within the database. A database user manual will be provided to sites.
Where an assessment has not been done or a particular value within an assessment is not available for any reason, there is an option for the site to record “not done”. Sites will be prompted to provide the reason via an automatic query generated by the database. If any data is changed after the initial completion of the eCRF, sites will be prompted to record the reason why.

Missing data for essential outcome variables and their subcomponents will be handled by multiple imputation by chained equation (MICE), incorporating longitudinal datapoints. Imputation will be performed five times and the mean (or median, if a particular variable is not Gaussian) result of imputation will be used to replace missing values. Imputed values will be checked for excessive variability across the five imputation runs.

15.0 Data handling and record keeping

15.1 Source data and source documents

Source documents include (but are not limited to): the patients' medical records, ECG printouts, laboratory reports, biopsy results, x-ray reports, patient questionnaires, and source data worksheets (which should be filed in the patient's medical records).

Direct access to source data will be granted to authorised representatives from the sponsor, host institution, and the regulatory authorities to permit study-related monitoring, audits, and inspections.

Each centre will be required to complete a Source Data Location agreement as part of the site initiation process in order to confirm the Source Data Locations for the assessments within the protocol.

15.2 Case Report Forms (CRFs)

Data collection will be in the form of completing electronic CRFs via the trial database to record all the required assessments at each study visit. The site study site team should aim to complete the CRF for each visit within one week of the visit date.

Please refer to the Database specification for all values collected within the eCRF, based on the Schedule of Assessments Table.

15.3 Data capture

Source data must be documented on source documents, such as source data worksheets, verified/signed lab reports or x-ray reports, medical notes and patient questionnaires. From these source notes, data is transcribed to the electronic database. When a participant is consented to the trial, the original consent form should be kept in the Investigator Site File, whilst a copy of the consent form should be given to the participant and a further copy should be kept in the participant's clinical notes/folder.

Each patient, at the time of consent, will be allocated a unique screening number by the database before undergoing any screening procedures. This information should be kept on a screening log, which should be updated accordingly throughout the study. Once the patient has completed screening procedures and is enrolled on the study, the patient will be allocated a randomisation number by the trial database.

Appropriate access to the database will be granted only to persons on the delegation log including central coordinating centre at EMR, each local site, and the Sponsor. Access levels will be granted in accordance with the staff members' delegated duties.

Regular data cleaning will be performed by the Coordinating centre to ensure the validity and quality of the data (please refer to the Data Management Plan for full details). An audit trail will be maintained in the database. Study site staff will be trained on the database at the Site Initiation Visit. There is also an e-CRF instruction manual. Study site training should be documented in the Site Initiation Report, and/or in training logs.

The eCRF will be encrypted at the point of the service user and will not provide identifiable data (only year of birth and initials) to the sponsor. The database will be hosted in the Bart's Cancer Institute, QMUL ITS Safe Haven datacentre. Please refer to the EMR QMUL Safe Haven hosting agreement for more information. Back-up of the database is described in detail in the EMR QMUL Safe Haven hosting agreement.

Access to the eCRF will be via an encrypted and password (multi-factor authentication (MFA)) protected link (SSL encryption). Only persons on the delegation log (site, central or Sponsor) will be given the appropriate access to the database.

The co-ordinating site will not hold any patient identifiable data. All clinical data will be stored in an encrypted format on the database, only viewable in a readable format by local trial staff and only for participants recruited at their site.

15.4 Transferring and transporting data

All data will be handled in accordance with the Data Protection Act (2018) and GDPR. No patient identifiable data will leave each hospital site. All data will be transferred from recruiting sites to the trial coordinating office as described previously.

15.5 Data Management

Immediate data cleaning will be performed following completion of the screening visit (visit 1) and biopsy visit (visit 2) of all data points prior to randomisation by the Trial Coordinating office. The subsequent data points will be regularly data cleaned throughout the trial. At the end of the trial, a final data clean will be performed and the PI will be required to sign -off to confirm the data is correct prior to database lock. The data cleaning, database lock and data export process is described in the Data Management Plan.

16.0 Confidentiality and De-identification of participants

The Chief Investigator will be the data custodian for all data generated during the study.

The Chief Investigator and the study team will ensure that all participants' identities are protected at every stage of the study. To ensure this, at time of consent each participant will be allocated a unique screening number by database before undergoing any screening procedures.

The Principal Investigator is responsible for protecting the identity of participants at their site. Participants will be referred to only by their unique study identifier whenever data is transferred outside of the site, and in all correspondence between the site and the coordinating centre, co-investigators, sponsor, or anyone associated with the study. An enrolment log will be kept in the investigator site file at each recruiting site to link the unique identifier to the patient.

Initials and year of birth only will be collected on the eCRF and in this patient population will not be considered identifiable data.

No participants will be individually identifiable from any publications resulting from the study.

Information regarding study participants will be kept confidential and managed in accordance with the Data Protection Act (2018), the UK Policy Framework for Health and Social Care and

Research Ethics Committee approval. All study data will be stored in line with the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments and the Data Protection Act. Study data will be archived in line with the Medicines for Human Use (Clinical Trials) Regulations 2004 and all subsequent amendments, and as defined in the JRMO SOP 20 Archiving.

Patients will be consented and will not own the results generated using the sample/s and data collected and in addition will not be entitled to any interest in or share of any profit that might arise from research using the sample/s or data.

17.0 Monitoring, Audit, and Inspection

17.1 Monitoring

A Trial Monitoring Plan will be developed and agreed by the sponsor and Chief Investigator based on the sponsor's risk assessment, which will include on site monitoring. Monitoring will be performed by the delegated personell within the EMR clinical team for the UK and EU sites. Monitor will be unblinded to the treat allocation. Monitoring procedures are detailed in the Trial Monitoring Plan.

17.2 Auditing

The sponsor retains the right to audit any aspect of the study, study sites, or central facilities. In addition, any part of the study may be inspected by the regulatory bodies, and funders where applicable.
All sites and vendors are asked to inform the sponsor if notified of any Audit or inspection affecting this study.

18.0 Compliance

The CI will ensure that the protocol and study is conducted in compliance with the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments, current UK Policy Framework for Social and health care research (2017), GCP guidelines, the World Medical Association Declaration of Helsinki, the Sponsor's and study specific SOPs, and other regulatory requirements.

The study will not commence until sponsor permission to activate sites is received.

Sites will be individually activated by the CI and team; this will not occur until site approval is granted.

The procedures are compliant with the Ionising Radiation (Medical Exposure) Regulations, and appropriate review by a Medical Physics Expert and Clinical Radiation Expert has been undertaken.

18.1 Non-Compliance

All deviations from the study protocol will be recorded at the Trail Coordinating Office and appropriate action will be taken. Deviation forms will be requested from sites where deemed necessary by the trial manager.

Non-compliances may be captured from a variety of different sources including monitoring visits, CRFs, communications and updates. The sponsor will maintain a log of non-compliances to ascertain if there are any trends developing which need to be escalated.

18.2 Notification of Serious Breaches to GCP and/or the protocol

A 'serious breach' is a breach which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the participants of the study; or
- The scientific value of the study.

The site Principal investigator is responsible for reporting any potential serious breaches to the sponsor (emrclinicaltrials@qmul.ac.uk) within **24 hours** of becoming aware of the event.

The Chief Investigator is responsible for reporting any potential serious breaches to the JRMO (research.safety@qmul.ac.uk) **within 24 hours** of becoming aware of the event.

The sponsor is responsible for determining whether a potential serious breach constitutes a serious breach, and will work with the CI to investigate and notify and report to the MHRA and REC (as applicable) within 7 working days of becoming aware of the serious breach.

EU sites
It is the responsibility of the lead site in each country to prepare and submit local forms to report Serious Breaches to their local ethical and regulatory bodies, as directed by the Sponsor.

19.0 Declaration of interests

TSC members are required to declare any competing interests and complete a competing interests declaration form.

20.0 Peer review

A scientific peer review has been conducted by IMI at the grant application stage of this project.

21.0 Public and Patient Involvement (PPI)

This study design and protocol outline were presented to PM-PAG (Precision Medicine Patient Advisory Group) during the protocol writing stage. The PM-PAG were also involved in the review of patient facing documents. There is a plan to ensure patients are involved throughout the duration of the study. In addition to a PPI group organised by the Chief Investigator, there will be an overarching 3TR PPI group.

22.0 Indemnity/ Insurance

The insurance that Queen Mary University of London has in place provides cover for the design and management of the study as well as "No Fault Compensation" for participants, which provides an indemnity to participants for negligent and non-negligent harm.

23.0 Study committees

23.1 Trial Management Group (TMG)

The Trial Management Group will include individuals responsible for the day-to-day management of the trial, such as the Chief Investigator, Statistician, Trial Manager, Research Nurse and Data Manager. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The TMG will meet monthly.

23.2 Trial Steering Committee (TSC)

The role of the Trial Steering Committee (TSC) will be to provide overall supervision on behalf of the Trial Sponsor and Trial Funder and to ensure that the trial is conducted to GCP and the relevant regulations. In particular, the TSC will concentrate on the progress of the trial, e.g. recruitment, adherence to protocol, patient safety and the consideration of new information of relevance to the research question. The TSC will be asked to comment in detail on extension requests or substantial changes to the protocol.

The TSC has membership from the TMG plus independent members, including the chair as detailed in the TSC terms of reference. The TSC membership is for the duration of the study. If any members leave the TSC, the CI (in collaboration with the TSC Chair and TMG) will provide replacements promptly for appointment by the chair.

Decisions about continuation or termination of the trial or substantial amendments to the protocol will be the responsibility of the Trial Steering Committee. The TSC will meet every 12 months during the recruitment phase of the study. The meetings may take the form of a teleconference or face to face meetings.

24.0 Publication and dissemination policy

24.1 Publication

It is anticipated that the results will be published in peer reviewed journals. Any investigator involved with this study is obliged to provide the Sponsor with complete results and all data derived from the study on request. Authorship of the final manuscript(s), interim publications, or abstracts will be decided according to active participation in the study design, trial management group and accrual of eligible patients. No participant may present data from his/her centre separately from the rest of the trial results unless approved by the CI/3TR-PARTNER-RA management group and the Sponsor.

All publications will be sent to the JRMO prior to publication. The full study report will be accessible via ISRCTN or ct.gov or other suitable public website within one year of the End of the Trial notification.

24.2 Dissemination policy

The sponsor owns the data arising from the study. Contributing centres (and participating investigators) will be acknowledged in the final manuscript. On completion of the study, data will be analysed and tabulated and a clinical study report will be prepared and submitted to the Ethics Committees.

24.3 Access to the final study dataset

The Coordinating site team will hold the final dataset for the study. Site investigators can access the full dataset if a formal request describing their plans is approved by the Chief Investigator and Trial Management Group (TMG) of this study.

25.0 Archiving

During the course of the research, all records are the responsibility of the Chief Investigator and will be kept in secure conditions. When the research study is complete, it is a requirement of sponsor Policy that the records are kept for a further 25 years.

Site files from other sites must be archived for 25 years at the external site and will not be stored at the Barts Health Modern Records Centre or within Queen Mary. Permission to archive will be issued by the Trial Coordinating Office once site closure has been completed.

Destruction of essential documents will require authorisation from the Sponsor.

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