Study Title: Optimising Psoriatic Arthritis Therapy with Immunological Methods to Increase Standard Evaluation

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Chief Investigator Signature: 

Statistician Signature: Approval of the protocol is documented in accordance with OCTRU Standard Operating Procedures

The Investigators declare they have no conflicts of interest relevant to this application

Protocol signatures continued

For multi-site research studies, the Principal Investigator at each site should sign below to document that the protocol has been read and understood before the protocol is filed in the site ISF. If the same PI covers more than 1 site both sites may appear here.

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Protocol signature page

The undersigned has read and understood the trial protocol detailed above and agrees to conduct the trial in compliance with the protocol.

Principal Investigator (Please print name)	**Signature**	**Site name**	**Date**

Following any amendments to the protocol, this page must be updated with the new protocol version number and date and re-signed by the site PI.

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1. KEY CONTACTS

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2. LAY SUMMARY

Our aim is to test whether we can predict if people with psoriatic arthritis (PsA) will respond to certain biologic drugs using blood tests. First, we will test if high levels of a type of T cells (activated Th17 cells) predict response to these treatments. Second, does combining this blood result with other laboratory tests or patterns of arthritis predict response more accurately? We will use statistical tests to estimate how effective these approaches are to select the biologic drug for each individual. If successful, this approach could ensure that patients receive their best option first, ensuring their disease is controlled more quickly and quality of life improved, while avoiding unnecessary drug use.

PsA is a type of inflammatory arthritis that develops in around 15% of people with the skin condition psoriasis, causing swollen and painful joints. It affects around 150,000 people in the UK. For patients who do not respond to standard arthritis drugs, two classes of biologic drugs are available (namely, TNF or IL-17A blockers). A similar proportion of patients respond to both with around 50% achieving a good response. However, we do not know how to predict in advance which patient will respond best to each of these drugs. A recent small study in Japan suggested that choosing the biologic drug based on patients' blood Th17 cells could give better results than the doctors' choice. However, they only did the blood tests in 28 people so we need to test this in a large study to see if this is reliable.

Patients with PsA about to start their first biologic will be invited to join the study. They will have a blood sample taken to analyse their T cells to see whether each patient has high or low levels of activated Th17 cells. The patients will be allocated equally to receive either TNF or IL-17 blocking biologics. We will measure how well they respond to the drug therapy after 6 months of treatment and test whether the initial blood result could have predicted their chance of responding.

If the test is able to predict the response to one or both of the drugs, we will then use statistical models to estimate how effective it would be if this blood test was used to choose the specific therapy. We will also combine this test with other blood results and the clinical pattern of a patient's arthritis to see if this further improves our ability to predict a good response.

3. SYNOPSIS

Study Title	Optimising Psoriatic Arthritis Therapy with Immunological Methods to Increase Standard Evaluation
Internal ref. no. / short title	OPTIMISE
Public Title	Can we predict which patients with Psoriatic Arthritis will respond to treatment using precision medicine?
Study registration	Registry name: ISRCTN registry Study identifier/ Registration number: ISRCTN17228602 Date of registration: 23 Mar 2021
Sponsor	RGEA, University of Oxford Joint Research Office, Boundary Brook House Churchill Drive Headington Oxford OX3 7GB E-mail: RGEA.Sponsor@admin.ox.ac.uk
Funder	National Institute of Health Research Efficacy and Mechanism Evaluation Grant NIHR 129023 Oxford Biomedical Research Centre (BRC) and Glasgow Core Funds (Sub- study).
Study Design	This is an open-label multi-centre, parallel-group, two arm randomised controlled study.
Study Participants	Adults (≥18 years old) with psoriatic arthritis confirmed by the CASPAR criteria who are planning to start biological therapy for their PsA following routine clinical practice.
Recruitment Target	268 (134 treated with TNF inhibitors, 134 treated with secukinumab)
Planned Study Period	01 December 2020 - 30 September 2026 Total study period - 70 months (9 months set up, 40 months recruitment, 6 months follow up, 15 months analysis and reporting). Each patient will be in the study for max 30 weeks (max 6 weeks screening to baseline + 24 weeks).
Planned Recruitment period	September 2021 to 31 December 2024

	Objectives	Outcome Measures	Timepoint(s)
Primary	To compare the response in participants to see whether it differs according to baseline CD4 T cell activated Th17 levels on the clinical response to TNF and IL-17A inhibitor therapy in PsA.	Clinical response as measured by the minimal disease activity (MDA) criteria	Immunophenotype data at baseline and clinical response at week 24.
Secondary	To compare the response in participants to see whether it differs according to intracellular IL17 levels, on the clinical response to TNF and IL-17A inhibitor therapy in PsA.	Clinical response as measured by the minimal disease activity (MDA) criteria	Immunophenotype data at baseline and clinical response at week 12/16 and 24.
	To understand if the activated Th17 surface and intracellular signature resolves after treatment with IL-17A blockade and how it is altered after TNF blockade.	Activated Th17 proportion and intracellular levels of IL-17	Immunophenotype data at baseline and week 24.
	To understand if changes in the activated Th17 surface and intracellular signature differ in treatment responders and non-responders.	Clinical response as measured by the minimal disease activity (MDA) criteria.	Clinical disease pattern and Immunophenotype data at baseline and clinical response at week 12/16 and 24.
	To explore if immune specific signatures can be used to predict response to IL-17A and TNF blocking therapies either alone or in combination with the activated surface and intracellular Th17 signatures.	Clinical response as measured by the minimal disease activity (MDA) criteria.	Clinical disease pattern and Immunophenotype data at baseline and clinical response at week 12/16 and 24.
	To explore if any of the baseline immune signatures are associated with response in different PsA tissues	Clinical response in PsA tissues including joint counts, enthesitis, dactylitis, skin and nail disease and in overall disease as measured by the PASDAS.	Immunophenotype data at baseline and clinical response at week 12/16 and 24.

	To explore if any of the baseline immune signatures are associated with response and disease impact from the patients' perspective	Response as measured by patient reported outcomes including PsAID, SF36 and WPAI	Immunophenotype data at baseline and clinical response at week 12/16 and 24.
	To use immune specific signatures to identify a limited number of molecular biomarkers that can be validated in whole blood.	Immune cell specific molecular signatures.	Immunophenotype data at baseline.
	To use immune specific signatures to define the pathways driving biologic-refractory disease.	Immune cell specific molecular signatures	Immunophenotype data at baseline and week 24.
Exploratory	See section 6 Objectives and Outcome Measures		
Intervention(s)	All patients will be treated with a biologic drug (TNF inhibitors (adalimumab) or IL-17A inhibitors (secukinumab) in keeping with routine clinical practice. At present both TNF inhibitors and IL-17 inhibitors are licensed and NICE approved as first line biologics in PsA. Patients will be randomised in a 1:1 ratio to receive either TNF or IL-17A inhibitors, stratified by baseline immunophenotype.		
Comparator	See above		

4. ABBREVIATIONS

BMI	Body mass index
BSA	Body surface area
BRC	Biomedical Research Centre
CASPAR	Classification Criteria for Psoriatic Arthritis
CI	Chief Investigator
CRF	Case Report Form
CRP	C- reactive protein
CTU	Clinical Trials Unit
DMARDs	Disease- modifying anti-rheumatic drugs
DSMC	Data and Safety Monitoring Committee
EME	Efficacy and Mechanism Evaluation
EULAR	European League Against Rheumatism
FBC	Full blood count
GCP	Good Clinical Practice
GP	General Practitioner
HAQ	Health assessment questionnaire
HIV	Human immunodeficiency virus
HRA	Health Research Authority
ICF	Informed Consent Form
IL-17	Interleukin 17
IL-17A	Interleukin 17A
IL-17Ai	Interleukin 17A inhibitors
LEI	Leeds enthesitis index
LFT	Liver function test
MAIT	Mucosal associated invariant T cells
MDA	Minimal disease activity
NICE	National Institute of Health and Care Excellence
NFT	NHS Foundation Trust
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NYHA	New York Heart Association
OCTRU	Oxford Clinical Trials Research Unit

PASDAS	Psoriatic Arthritis Disease Activity Score
PASI	Psoriasis Area Severity Index
PSAID	PsA impact of disease
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
PIC	Participant Identification Centre
PsA	Psoriatic arthritis
PSP	Priority setting partnership
RA	Rheumatoid arthritis
REC	Research Ethics Committee
RGEA	Research Governance, Ethics & Assurance
RNA	Ribonucleic acid
SMC	Scottish Medicines Consortium
SOP	Standard Operating Procedure
SPARCC	Spondyloarthritis Research Consortium of Canada
TB	Tuberculosis
Th17	T helper cells with 17 signature
TNF	Tumour necrosis factor
TNFi	Tumour necrosis factor inhibitors
UKCRC	UK Clinical Research Collaboration
U&E	Urea and electrolytes
VAS	Visual analogue scale
WS	Work stream
WPAI	Work productivity and activity impairment

5. BACKGROUND AND RATIONALE

Psoriatic arthritis (PsA) is an inflammatory arthritis that occurs in ~15% of people with psoriasis, affecting around 150,000 people in the UK[1]. Two-thirds of people with PsA suffer joint damage with associated disability [2] similar to rheumatoid arthritis (RA) [3]. PsA is associated with reduced life expectancy [4] and average direct healthcare costs of £2,400 per patient with indirect costs of >£8,000 annually [5].

The current treatment of PsA follows a 'step up' 'trial-and-error' approach using different conventional disease-modifying anti-rheumatic drugs (DMARDs) followed by biologics if patients do not respond [1 6]. Approximately 50% of patients require biologic therapy [7]. The current first line biologic treatments for PsA target two main immunological pathways:

1. Tumour necrosis factor inhibitors (TNFi) - monoclonal antibodies or receptor antagonists blocking the action of TNF, a key predominantly myeloid-derived cytokine involved in immune cell trafficking and maintenance of the inflammatory response.
2. Interleukin (IL) 17 inhibitors - monoclonal antibodies targeting IL-17A which plays a pleotropic role in inflammation including recruitment of neutrophils and bone erosion[8].

Response rates to both drugs are similar with around 60% of patients achieving a minimal response. However, 50% fail to achieve the therapeutic target of treatment defined by the minimal disease activity (MDA) criteria[9 10]. Patients not achieving MDA have worse quality of life, ongoing joint damage, functional impairment and high impact on their participation and ability to work [10]. In clinical practice, biologic therapies require use for a minimum of 12 (TNFi) or 16 weeks (IL-17Ai) before response can be evaluated[1 6] and MDA is assessed even later (24 weeks)[11]. For patients this means a long delay on a therapy that may never work.

Whilst having different therapeutic options is welcome, there is currently no evidence to guide biologic choice in PsA. We know that some people who fail to respond to a first line biologic will have a good response when they switch to a drug with a different mechanism of action[12] suggesting that disease pathogenesis varies between individuals. Currently we cannot predict who will respond to each therapy resulting in delays on ineffective therapies associated with negative impact on patients' lives and a high cost burden to the NHS.

Currently in clinical practice we select either TNF or IL-17A inhibitors for patients with moderate-severe active PsA based on a limited clinical phenotype (differentiation in psoriasis has been shown), comorbidities, personal experience and cost. In the UK, most patients currently receive TNF inhibitors first line, presumably due to longer term data, physician familiarity and lower cost using biosimilars. However, the Th17 pathway is significantly upregulated in PsA. Th17 cells are a subset of pro-inflammatory T helper cells defined by their production of IL-17, thus suggesting that treatment with IL-17 inhibitors in some individuals could improve outcomes. The lack of data informing the choice of biologics is frustrating for clinicians and for patients who want to know which therapy would be best for them. There has not been a James Lind priority setting partnership (PSP) for PsA however in the recent Psoriasis PSP the question "What factors predict how well psoriasis will respond to a treatment?" was ranked 3rd in the top ten unmet needs. This highlights the importance that both patients and clinicians ascribe to the issue.

It is increasingly recognised that to optimise quality of life and functional ability, treatment should be focused on achieving a treatment target, such as MDA. Patients who achieve MDA have less joint damage as measured using x-rays, better quality of life and function[10]. Thus optimising an individual's

outcomes, requires the ability to predict which biologic has the greatest chance of that individual achieving MDA and then utilising this precision medicine approach in routine clinical practice.

This study will test the hypothesis that activated Th17 cell levels can predict response to therapy and elucidate the mechanistic basis of this approach. This study is using two different proven PsA therapies with extensive data from phase 2-4 clinical trials. The primary clinical outcome is a recommended target of treatment in PsA with confirmed prognostic ability. The biomarker used for stratification in this study has proof of concept in a small RCT from Japan[13], but has been refined using UK patient data to account for potential genetic differences from the Japanese population. In addition to the principal biomarker, a number of additional biomarkers with supportive data from ex-vivo studies will be tested using novel bioinformatic approaches which have proven successful in other immune-mediated inflammatory conditions This data will provide modelled proof of clinical effectiveness for a precision medicine approach to prospectively select biological therapies in individuals with PsA. This approach could easily be implemented into routine NHS practice as both drugs are already NICE approved for use in PsA. Transforming our treatment algorithms in PsA getting the right drug to the right patient the first time will result in rapid control of inflammation, resulting in improvements in patients' function, work participation and quality of life. Optimising drug selection will also provide cost savings to the NHS avoiding unnecessary primary non-response to therapies.

6. OBJECTIVES AND OUTCOME MEASURES

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objective To compare the response in participants to see whether it differs according to baseline CD4 T cell activated Th17 levels, on the clinical response to TNF and IL-17A inhibitor therapy in PsA.	Clinical response as measured by the minimal disease activity (MDA) criteria	Immunophenotype data at baseline and clinical response at week 24.
Secondary Objectives To compare the response in participants to see whether it differs according to intracellular IL-17 levels, on the clinical response to TNF and IL-17A inhibitor therapy in PsA.	Clinical response as measured by the minimal disease activity (MDA) criteria	Immunophenotype data at baseline and clinical response at week 12/16 and 24.
To understand if the activated Th17 surface and intracellular signature resolves after treatment with IL-17A blockade	Activated Th17 proportion and intracellular levels of IL-17	Immunophenotype data at baseline and week 24.

and how it is altered after TNF blockade.		
To understand if changes in the activated Th17 surface and intracellular signature differ in treatment responders and non-responders.	Clinical response as measured by the minimal disease activity (MDA) criteria.	Clinical disease pattern and Immunophenotype data at baseline and clinical response at week 12/16 and week 24.
To explore if immune specific signatures can be used to predict response to IL-17A and TNF blocking therapies either alone or in combination with the activated surface and intracellular Th17 signatures.	Clinical response as measured by the minimal disease activity (MDA) criteria.	Clinical disease pattern and Immunophenotype data at baseline and clinical response at week 12/16 and week 24.
To explore if any of the baseline immune signatures are associated with response in different PsA tissues	Clinical response in PsA tissues including joint counts, enthesitis, dactylitis, skin and nail disease and in overall disease as measured by the PASDAS.	Immunophenotype data at baseline and clinical response at week 12/16 and 24.
To explore if any of the baseline immune signatures are associated with response and disease impact from the patients' perspective	Response as measured by patient reported outcomes including PsAID, SF36 and WPAI	Immunophenotype data at baseline and clinical response at week 12/16 and 24.
To use immune specific signatures to identify a limited number of molecular biomarkers that can be validated in whole blood.	Immune cell specific molecular signatures	Immunophenotype data at baseline.
To use immune specific signatures to define the pathways driving biologic-refractory disease.	Immune cell specific molecular signatures	Immunophenotype data at baseline and week 24.
Exploratory Objectives To use machine learning and predictive modelling to combine baseline clinical phenotypic markers such as disease duration and clinical expression of disease	Clinical response as measured by the minimal disease activity (MDA) criteria.	Clinical disease pattern and Immunophenotype data at baseline and clinical response at week 24.

with additional immunophenotypical (intracellular CD4 Th17 frequency, CD8 Tc17 frequency, MAIT cell frequency, immune molecular signature) factors to develop a predictive model for response to IL-17A and/or TNF inhibitor therapy in PsA.		
To compare the response in participants to see whether it differs according to baseline CD4 T cell activated Th17 levels on the clinical response to TNF and IL-17 inhibitor therapy in PsA.	Clinical response as measured by the minimal disease activity (MDA) criteria	Immunophenotype data at baseline and clinical response at week 12/16.
To explore if the change or absolute levels of activated Th17 surface and intracellular signature or the molecular signatures at week 4 can predict response to IL-17A and TNF blocking therapies	Clinical response as measured by the minimal disease activity (MDA) criteria.	Immunophenotype data at baseline and 4 weeks and clinical response at week 12/16 and 24.
To explore changes in synovial tissue and fluid immunology pre and post treatment and see if this correlates with clinical outcome and/or blood markers described above	Clinical response as measured by the minimal disease activity (MDA) criteria.	Synovial biopsy analysis at baseline and 24 weeks

7. STUDY DESIGN

This is an open-label multi-centre, parallel-group, biomarker-stratified two arm randomised controlled trial recruiting adults (≥18 years old) with psoriatic arthritis confirmed by the CASPAR criteria who are planning to start biological therapy for their PsA following routine clinical practice. It will be performed within rheumatology departments at the participating hospitals within the NHS, with sample analysis taking place at associated University research facilities at the University of Oxford, King's College London, and University of Glasgow.

A total of 268 patients eligible for treatment with their first biologic for PsA as part of their standard NHS care will be approached for inclusion. All patients will be required to fulfil the NICE/SMC or the local guidelines for eligibility for biologics in PsA which include the failure of ≥1 conventional DMARDs and the presence of active disease with a minimum of 3 tender and 3 swollen joints. Following consent, patients

will undergo a baseline clinical assessment and blood will be taken for immunophenotyping. We will record the therapy that was planned by the physician if they had not been recruited to the trial, prior to their randomisation to be used in subsequent modelling to estimate the additional benefit of any precision medicine test developed. Each participant will be in the study for a maximum of 30 weeks (max 6 weeks screening to baseline and 24 weeks treatment and follow up). During this time, there will be 3 or 4 study visits. All participants will attend once for screening and twice for follow up, with participants at the hub sites attending an additional visit for sample collection. Composite clinical outcome measurements will be collected via an electronic CRF to assess response to treatment. These will include validated questionnaires of disease activity and impact and clinical assessments of disease activity by a member of the study staff. To avoid bias from treatment class, the primary clinical measures will be assessed by a blinded member of the study team. The baseline immunophenotype data will be blinded from all clinical study site personnel, while laboratory staff will be blinded to the allocated therapy. Trial office staff not directly involved with patient care will be unblinded and will enter immunophenotype results into the randomisation system. This will ensure that the primary research question is answered based on blinded data and therefore the open label treatment does not represent a risk of bias.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

The population targeted are adults (≥18 years old) with psoriatic arthritis confirmed by the CASPAR criteria who are planning to start biological therapy for their PsA following routine clinical practice.

8.2. Inclusion Criteria

All participants should fulfil the following:

- Participant is willing and able to give informed consent for participation in the study
- Male or female, Age 18 years or over
- Diagnosis of PsA confirmed by the CASPAR criteria [30]
- Is eligible and planned to have biologic therapy for psoriatic arthritis using local guidelines or using NICE/SMC criteria (failure of ≥1 csDMARDs and ≥3 tender AND ≥3 swollen joints).

8.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Contraindications to either TNF inhibitor or secukinumab (determined by clinical team prior to recruitment):
    - History of previous demyelinating disease including multiple sclerosis
    - Heart failure (NYHA class 3 or 4)
    - Serious infections: active tuberculosis (TB), chronic viral infections (including hepatitis B, C and HIV), recent serious bacterial infections

  - Latent TB unless they have received appropriate anti-tuberculous treatment as per local guidelines
  - Active symptomatic inflammatory bowel disease
  - History of cancer in the last 5 years, other than non-melanoma skin cell cancers cured by local resection or carcinoma in situ
  - Hypersensitivity to active ingredient or excipients
- Current or previous treatment with biologic DMARDs or targeted synthetic DMARDs, except for Apremilast.
- Use of investigational therapies within 1 month or 5 half-lives (whichever is longer) of baseline.
- Women who are pregnant, lactating or planning pregnancy during the following 12 months or who are unwilling to follow standard of care contraceptive advice.
- Received COVID-19 vaccination in the 2 weeks prior to screening visit.

9. PROTOCOL PROCEDURES

9.1. Recruitment

The three hub sites for the study (those with an associated research laboratory undertaking study specific analysis of research samples) are: Oxford University Hospital NFT, Glasgow Royal Infirmary (NHS Greater Glasgow & Clyde), Guy's and St Thomas' NFT (London).

Additional participating centres will be selected from NHS Trusts with clinical capacity to undertake the study and located such that samples can be transported to one of the hub sites within the time frame specified in the OPTIMISE Sample Handling Manual.

Participants will be identified from rheumatology clinics in the participating centres. They will be approached first by their treating physician or a member of the clinical care team. They will usually be given information by their treating physician during a consultation about biologic initiation but may be contacted by telephone by the clinical nurse specialists or other clinical team members prior to their prescription for biologics if they are not approached earlier. In some cases, potential participants, identified at Participant Identification Centres (PIC), will be provided with the PIL and if interested in the study, referred to one of the participating centres where protocol- related procedures (screening, consenting, and follow-up) will take place.

Once a potential participant, identified by these means, confirms their interest in the study, they will be provided with a PIL and an opportunity to discuss their eligibility and the details of the study. All potential participants will receive the PIL and will have an opportunity to discuss the study with an investigator as part of the informed consent process during the first study visit. Given the very minimal burden and risk of study participation to participants compared with standard care, there is no minimum time required between approach and consent; therefore potential participants may be approached and consent to the study at the same clinic visit.

9.2. Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. However, the decision to participate in the study should not delay treatment so we advise that potential participants are given no longer than 1 week to decide. Written Informed Consent will then be obtained by means of participant-dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site, with a copy stored in the patient's hospital notes/electronic record. For those participants who have agreed to the optional consent clause of future use of samples, a copy should be sent to the trial office and will be retained by the University of Oxford until the sample has been depleted or destroyed, to meet the traceability requirements of the Human Tissue Act.

Consent will include consent for the participant's GP to be informed of their involvement in the study. Following randomisation the GP letter must be sent by the site team to the participant's GP.

9.3. Screening and Eligibility Assessment

The maximum duration between screening and randomisation will be 6 weeks. There will be no exceptions made regarding eligibility and all participants must satisfy all of the approved inclusion and exclusion criteria within the protocol. Rescreening will be permitted.

Screening Visit

Following consent, all patients screened for the study will be registered on the OCTRU study registration system using the automated, secure, 24 hour internet and phone (office hours only) service. This will generate a unique study number for the electronic CRF and to label the blood samples and will subsequently be used throughout the study.

The following will be performed at the visit and recorded in the eCRF, with appropriate information also documented in the patient's notes. Patients will undergo a clinical assessment to assess eligibility for the study and baseline disease activity. The following will be performed at the visit:

Medical history (10 mins):

Obtain from medical record, or, where not undertaken as part of routine care:

- Record demographics.
- Obtain psoriasis history: phenotype; disease duration and PsA type and disease duration.
- Check concomitant medication (glucocorticoids and non-steroidal anti-inflammatory drugs only).
- Record previous/current conventional systemic DMARD treatments

- Record the therapy that was planned by the physician if they had not been recruited to the trial.
- Record history of alcohol intake and diabetes.
- Check previous medical history to ensure eligibility
- CASPAR Criteria[14]
    - Evidence of current psoriasis
    - Personal history of psoriasis
    - Family history of psoriasis
    - Psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis
    - Evidence of current or documented history of dactylitis
    - Rheumatoid factor negative
    - Evidence of new bone formation on radiographs.

For those patients for whom no reason for ineligibility is identified, the following are then to be undertaken:

Composite Clinical Outcome Measures (20 mins)

- Full clinical disease assessment:

In addition to the **Tender and Swollen Joint Count** (a full 68 tender and 66 swollen joint count, replaced joints will not be counted) and **Physician's VAS of overall disease activity** that is done as part of routine care, the following are to be undertaken for the study where not done as part of routine care:

    - Dactylitis Assessment using count of tender dactylitic digits
    - Enthesitis Assessment using Leeds enthesitis index [15] and the Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index [16]
    - Psoriasis Area Severity Index (PASI) [17] and body surface area (BSA) [18]
    - Nail psoriasis VAS

- Patient reported outcomes (30 mins):

In addition to the **Global disease activity visual analogue scale (VAS)** [19] that is done as part of routine care, the following are to be undertaken for the study where not done as part of routine care:

    - Participant pain VAS
    - Health assessment questionnaire (HAQ) [20]
    - PsA impact of disease (PSAID) [21]
    - SF36 [22]
    - Work productivity and activity impairment (WPAI) [23]

Anthropometric measurements (5 mins)

Where not undertaken as part of routine care:

- Measure height and weight of the participant to calculate BMI.
- Take hip and waist measurements.

Routine clinical investigations for safety of therapies (5 mins)

These clinical safety checks will be performed as part of routine care but checked for the trial participants at baseline to ensure they are safe to start treatment.

- Routine clinical blood tests (FBC, U&E, LFT, CRP). Note: must be checked at this visit regardless of when last tested.
- Standard safety screening for biological therapies as per local guidelines (hepatitis, HIV and TB screening) to include blood tests and chest radiograph as advised.

Immunophenotyping blood tests (taken alongside routine bloods above)

- Collection of blood samples (80 mls) for immunophenotyping (see section 9.9 for details). *Note*: samples must arrive at laboratory within the time specified in the OPTIMISE Sample Handling Manual.

The immunophenotyping blood sample will be collected and processed simultaneously with standard safety screening for biological therapies (e.g. hepatitis/TB screening), avoiding delay to patients' treatment.

Each recruiting centre will maintain an anonymised log of all patients approached for the trial including those who declined participation or were found to be ineligible during screening. This will allow an assessment of the generalisability of the trial results, in accordance with CONSORT guidelines.

Ultrasound guided synovial biopsy (optional procedure only available at some sites)

In those patients who have consented to have synovial tissue and fluid collected a musculoskeletal ultrasound will be carried out to assess whether there is sufficient synovial tissue for biopsy. Ultrasound is widely used in the routine assessment of disease. It is safe, well tolerated and carries no radiation risk. There is increasing evidence of the utility of ultrasound in disease assessment, patient stratification and prognostication. Ultrasound of the swollen knee, wrist or metacarpal joint will take no more than 15 minutes to complete, and will assess the eligibility for biopsy.

Synovial fluid and small synovial tissue samples will be collected using ultrasound guidance to investigate biological effects of the study interventions (Appendix C). This procedure is minimally invasive and will be conducted under local anaesthesia. This procedure will be performed by trained staff in our dedicated Clinical Trials Unit. Each biopsy procedure takes approximately one hour to complete. Participants are able to drive home and self-care independently afterwards. Ultrasound guided synovial biopsy is very well tolerated but rarely may be complicated by the following:

- Joint infection (0.1%)
- Bleeding into the joint (0.1%)
- Wound infection (0.1%)
- Deep vein blood clot (0.2%)
- Nerve damage (0.02%)
- Vein inflammation (0.08%)

The procedure will be completed at the same time as the screening visit, if feasible. If not, an additional appointment will be arranged for the biopsy to be taken.

9.4. Randomisation

Once all eligibility data and immunophenotyping results are available, randomisation will be performed centrally by CTU staff following confirmation of eligibility from study site personnel, using the OCTRU randomisation system. Patients will be randomised in a 1:1 allocation ratio to either TNF or IL-17A inhibitors and these drugs will be prescribed open label as in routine care. The randomisation will use a minimisation algorithm to ensure balanced allocation across the treatment groups, stratified by activated Th17 proportion (≤/>1.58%), psoriasis severity (PASI < or ≥10) and study centre. The minimisation algorithm will include a probabilistic element and a small number of participants randomised by simple randomisation at the start of the trial to seed the algorithm in order to ensure the unpredictability of treatment allocation. Patients will be contacted by telephone to confirm continued consent to participate and to advise them of their treatment allocation.

There is no blinding of therapy allocation so no allocation code or code-breaking procedure is required. All relevant study personnel will be informed of the treatment allocation by email.

Following randomisation the GP letter must be sent by the site team to the participant's GP to notify them of study participation and treatment allocation.

9.5. Blinding and code-breaking

There is no blinding of therapy allocation in this study.

9.6. Description of study intervention(s), comparators and study procedures (clinical)

9.6.1. Description of study intervention(s)

Following the screening visit and subsequent randomisation, patients will receive either a TNF or IL-17A inhibitor according to the randomisation allocation. These will be given open label at the usual licensed dose and patients will be taught to self-administer the treatments as in usual NHS practice.

TNF inhibitor – Adalimumab

The TNF inhibitor to be used is adalimumab (any brand) and it is to be given at the usual licensed dose, as per the SmPC:

- The licenced dose of adalimumab for psoriatic arthritis is always 40 mg by subcutaneous injection every 2 weeks, with no loading doses.

Adalimumab is to be provided from usual NHS stock and will be administered by the patients following initial training.

IL-17A inhibitor – Secukinumab

The IL-17A inhibitor to be used is secukinumab, brand name Cosentyx, and is to be given at the usual licensed dose as per the SmPC:

- The licensed dose of secukinumab for psoriatic arthritis varies based on the level of baseline skin psoriasis. For patients with concomitant moderate to severe plaque psoriasis, the recommended dose is 300mg by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4 followed by

a monthly maintenance dose. For other patients the recommended dose is 150mg by subcutaneous injection at the same timepoints. This study will follow routine practice and the current label by using the appropriate dose of secukinumab based on the baseline psoriasis disease activity with the cut off for moderate to severe psoriasis as 10% body surface area. Dose escalation as per the licence is permitted.

Secukinumab is to be provided from usual NHS stock and will be administered by the patients following initial training.

Drug treatment will be continued for the 24 weeks with assessments at baseline, week 12 (for those on adalimumab) or week 16 (for those on secukinumab) and 24 weeks (for both) in keeping with current clinical practice and NICE guidance. After the 24 week study treatment period, participants who have responded well to treatment can continue on treatment off-study or switch to another treatment in line with usual NHS practice.

9.6.2. Description of study procedure(s)

Clinical procedures within the study will include physical examination, questionnaires and blood sample collection. Routinely collected data will also be collected on the study CRFs from the patient's notes. The physical examination and questionnaires will be combined to calculate key composite clinical outcome measures including the MDA criteria (the primary outcome). These will be performed at screening, week 12/16 and week 24. Blood samples will be collected at screening, week 12/16 and week 24, with an additional immunophenotyping sample taken at week 4 for patients under the care of the hub sites.

Composite Clinical Outcome Measures – see section 9.3.

Routine clinical investigations for safety of therapies – see section 9.3.

Immunophenotyping blood tests (taken alongside routine bloods above) – see section 9.9.

9.7. Baseline Assessments

Baseline clinical assessments and questionnaires will be completed at the screening visit and will be used to measure pre-treatment disease activity.

Following the screening visit, eligibility will be confirmed for the study and randomisation will be performed as outlined in section 9.4. The patient will be informed of the drug that they have been randomised to and a routine NHS prescription for that drug (either adalimumab or secukinumab) will be submitted by the clinical care team. Treatment will be started following standard NHS procedures (which usually takes 3-4 weeks from the prescription being written). In most cases, this will mean that NHS drug supply will be delivered to the patient by an approved healthcare delivery company to ensure temperature control. The patient will be trained how to perform the injections themselves and how to safely dispose of any sharps as per usual practise at each participating site. This may be done by telephone or video call as per usual practise at each participating site. The patient will administer the treatment themselves.

The baseline date will be the date that the drug is first administered.

9.8. Subsequent Visits

9.8.1. Week 4 – hub sites only

All participants attending the hub sites in Oxford, Glasgow, Guy's and St Thomas' NFT London (up to 100) will attend to enable an additional blood sample for research to be obtained (see section 9.9).

This visit is the only study visit that is additional to standard clinical care and no additional clinical data will be collected at this visit.

9.8.2. Week 12 or 16 – all sites

Participants will attend at week 12 (TNFi [adalimumab] treated patients) or 16 (IL-17Ai [secukinumab] treated patients) in line with routine care. The following will be performed at the visit for the purpose of the study:

Update of medical history (5 mins):

Where not undertaken as part of standard care:

- Confirm any key changes in their medical history
- Record change in concomitant medication (glucocorticoids and non-steroidal anti-inflammatory drugs only).
- Experience of any key side effects to medication

Composite Clinical Outcome Measures (20 mins plus 30 min for questionnaire completion)

- as baseline assessment (screening visit) – see section 9.3.

Medication compliance (2 mins)

- Any patient-reported missed doses of treatment will be recorded.

The study visit would take ~60 minutes compared to 15 minutes for a routine care visit.

9.8.3. Week 24 – all sites

Participants will attend at week 24 in line with routine care. The same assessments as per the week 12/16 visit will be performed at the visit plus collection of a research blood sample from the participants attending the hub sites (Oxford, Glasgow, Guy's and St Thomas' NFT London) (up to 100) (see section 9.9).

The study visit would take ~60 minutes compared to 15 minutes for a routine care visit.

9.9. Sample Handling

9.9.1 Sample handling for study purposes
Peripheral blood sample

Fresh peripheral blood samples (80 ml) will be collected from all participants at screening, and additionally from up to 100 participants attending the 3 hub sites (Oxford University Hospital, Glasgow Royal Infirmary, Guy's and St Thomas' NFT London) at 4 weeks and 24 weeks for analysis.

These blood samples will be transported to one of the three laboratory centres (University of Oxford, University of Glasgow, King's College London [all UK]) for processing. Samples need to arrive at the

laboratory within the time specified in the OPTIMISE Sample Handling Manual. See sample handling manual for further details.

Samples will be used for a number of analyses that will be undertaken at different times in the study including eight colour flow cytometry. Samples will be split into individual aliquots for different purposes, with these aliquots being distributed to and then used/stored at all three of the laboratory centres. All sample handling will be performed following trial-specific standard operating procedures. Antibodies used and flow cytometer optimisation will be standardised across the sites to ensure consistent results.

To obtain the immunophenotyping results required for randomisation, activated Th17 cells will be identified based on CCR6 and CXCR3 expression on CD4 T cells and co-expression of known T cell activation markers CD38 and HLA-DR, as described in the Miyagawa study[13]. This activated Th17 proportion (≤/>1.58%) from baseline samples will be included in the randomisation process to ensure equal stratification across the RCT arms.

In parallel, we will perform intracellular cytokine staining of IL-17A/F and interferon gamma in CD4, CD8 and MAIT cells to further elucidate the mechanisms of disease.

Aliquots of the research blood samples will be stored frozen at the three lab centres for subsequent in–depth molecular interrogation on whole blood baseline samples to identify additional predictors of response. Using predefined machine learning techniques that generated predictive signatures in SERA[27]- these data will be incorporated in the second and third stage analysis detailed below. On a subset of samples (20 high Th17 and 20 low Th17) we will also perform cell sorting and molecular characterisation on isolated CD4, CD8, CD14 and NK cells in order to understand the cell-specific molecular predictors of response and refractory disease. Processing of samples for molecular characterisation may be undertaken at the laboratory centres or may be outsourced to external service providers under appropriate contracts.

The same analysis will be repeated at 4 weeks and 24 weeks on patients recruited from the 3 hub sites (up to 100 to examine the effect of therapy and relate this to clinical response. Samples collected will be prepared and frozen for analysis.

Samples may also be stored long term for analysis outside of this study. Consent (optional) will be sought from all participants for long term storage and future use of samples. Any sample destruction will be done in with HTA requirements.

Synovial Fluid & Tissue

Optional synovial samples (as many as possible) will be collected from participants attending the 2 sites (Oxford University Hospital & Glasgow Royal Infirmary) at screening and week 24 visit as described in Appendix C

Synovial samples will be stored frozen at the two associated laboratory centres (Oxford University & University of Glasgow) until analysis. Synovial fluid & tissue handling procedures are detailed in Laboratory Manual for Synovial Samples.

Synovial samples will be used for a number of exploratory analyses.

9.10. Early Discontinuation/Withdrawal of Participants

During the course of the study a participant may choose to withdraw early from the study treatment at any time. This may happen for several reasons, including but not limited to:

- The occurrence of what the participant perceives as an intolerable AE.
- Inability to comply with study procedures
- Participant decision

Participants may choose to stop treatment and/or study assessments but may remain on study follow-up. Participants may also withdraw their consent, meaning that they wish to withdraw from the study completely.

According to the design of the study, participants may have the following two options for withdrawal;

1) Participants may withdraw from active follow-up and further communication but allow the study team to continue to access their medical records and any relevant hospital data that is recorded as part of routine standard of care.

2) Participants can withdraw from the study but permit data and samples obtained up until the point of withdrawal to be retained for use in the study analysis. No further data or samples would be collected after withdrawal.

In addition, the Investigator may discontinue a participant from the study treatment at any time if the Investigator considers it necessary for any reason including, but not limited to:

- Adverse Event
- Pregnancy
- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- Clinical decision

If participants withdraw/are withdrawn from treatment, then standard follow up in NHS clinics will be used to ensure safety, but no further study visits would be required.

Wherever possible the data of randomised participants should be analysed. Withdrawal from the study treatment will not result in exclusion of the data for that participant from certain analyses. Participants will not be replaced. The type of withdrawal and reason for withdrawal (if known) will be recorded in the CRF.

If the participant is withdrawn due to an adverse event, the Investigator will arrange for follow-up at clinic visits or by telephone calls until the adverse event has resolved or stabilised.

Sites are reminded that if a patient withdraws/is withdrawn from treatment, it is not necessary for the participant to be withdrawn from future study follow up, unless this is necessary (i.e. participants requests, or due to non-attendance).

9.11. Definition of End of Study

The end of study is the point at which all the study data has been entered and queries resolved including the data generated from the laboratory analyses.

10. SAFETY REPORTING

Safety reporting is applicable to this study, and the safety reporting window will be from time of consent, until the point that the participant completes the study (i.e., attends the week 24 visit). Investigator follow up of SAEs will be until participant completion of the study.

10.1. Definitions

Definition of Adverse Event (AE)

Any untoward medical occurrence in a clinical trial participant.

Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. This includes 'transmission of infectious agents via a medicinal product' if this does not fall into one of the other categories specified above.

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.

10.2. Reporting Procedures for Serious Adverse Events

Sites are required to report to the OPTIMISE trial team only those SAEs that are related to trial intervention (i.e. secukinumab or adalimumab) or trial procedures. These SAEs must be reported within a very short period of time and under no circumstances should this exceed 24 hours following knowledge of the SAE.

Causality of the SAE with respect to trial intervention/procedures must be assessed by medically qualified doctor according to the following definitions, however this may be missing at the time of the initial report of the SAE:

Classification	Relationship	Definition
Related	Almost certainly	Starts within a time related to the trial drug administration

		and No obvious alternative medical explanation.
	Probably	Starts within a time related to the trial drug administration *and* Cannot be reasonably explained by known characteristics of the participant's clinical state.
	Possibly	Starts within a time related to the trial drug administration *and* A causal relationship between the trial drug and the adverse event is at least a reasonable possibility.
Not related	Unlikely	The time association or the participant's clinical state is such that the trial drug is not likely to have had an association with the observed effect.
	Unrelated	The AE is definitely not associated with the trial drug administered.

SAEs are to be reported to the OPTIMISE trial team via completion of the OPTIMISE SAE form, which should be scanned and emailed to: optimise@ndorms.ox.ac.uk. Receipt will be acknowledged within 1 working day.

Expectedness will be determined by the Nominated Person at OCTRU on behalf of the Sponsor. Expectedness for events reported as related to adalimumab or secukinumab will be determined in relation to the version of the SmPC specified in the REC application for these drugs.

SAEs reported as related to other trial procedure will be deemed as unexpected.

A serious adverse event (SAE) occurring to a participant will be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures include study drug treatment) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs will be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website). This will be undertaken by the OPTIMISE trial team at OCTRU.

10.3. Contraception & Pregnancy

Contraception advice is to be given as per standard of care.

In the event that a trial participant becomes pregnant, the pregnancy is to be managed as per standard of care.

Pregnancy does not require to be reported to the OPTIMISE trial team other than in the unexpected occurrence of a pregnancy with an unfavourable outcome (congenital abnormality or birth defect) which is deemed related to trial treatment, in which case this requires to be reported as a SAE.

11. STATISTICS AND ANALYSIS

11.1. Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here with details fully described in a statistical analysis plan that will be available from the time that the first participant is recruited. The SAP will be finalised before any analysis takes place.

11.2. Description of the Statistical Methods

The primary clinical response outcome will be the achievement of the MDA criteria. This is a dichotomous composite criteria including clinical outcomes (tender joint count, swollen joint count, enthesitis count and psoriasis score) and patient reported outcomes (patient global score, patient pain score and function measured by the HAQ. To be classified as being in MDA, patients must achieve 5 or more of the criteria given below:

Domain	Measure Used	Criteria for assessing MDA
Peripheral arthritis	Tender joint count (68)	≤1
Peripheral arthritis	Swollen joint count (66)	≤1
Enthesitis	Enthesitis count (LEI and SPARCC)	≤1
Psoriasis	PASI	≤1
Pain	Patient pain VAS	≤15mm
Global disease activity	Patient global VAS	≤20mm
Function	HAQ	≤0.5

The proportion of patients achieving the criteria in the Th17 high vs Th17 low groups will be compared within treatment arms. Primary analysis will be logistic regression adjusted for Th17 as a continuous indicator, treatment and an interaction between the 2. We will also adjust for the stratification factors study centre and psoriasis severity. A random effect will be included to account for any heterogeneity in the response due to recruitment centre, with the other variables being incorporated as fixed effects. Primary focus is on the interaction between biomarker and treatment, we will report the p-value for this interaction and consider a p-value < 0.05 as significant. We will report the mean response rate by treatment and also for each of the 4 strata defined by treatment and biomarker along with 95% CI. Analysis will be on an intention to treat basis, that is according to group randomised to irrespective of compliance with treatment allocation.

Additional hypothesis generating analyses will be undertaken to investigate alternative potential models for predicting response to different classes of biologic. The data will be used to model response rates adjusting for other variables (for example: different therapies (TNFi vs IL-17i), standard care (the therapy originally planned by the recruiting physician), alternate cut-off points of Th17 proportions, Th17 proportions as a continuous measure or alternative laboratory measures of immunophenotype including epigenomics. We will be able to use the models developed to predict what outcomes would be expected from a precision medicine based clinical pathway. This could then be validated in a future study.

For the explorative objectives we will use the immunophenotyping and epigenomic data generated to gain mechanistic insight into genes and pathways that underpin the clinical response. Analysis of paired flow cytometry samples before and after treatment in each arm will allow us to understand the stability of the Th17 compartment in MDA responders and non-responders. This question is especially pertinent in view of data suggesting the intracellular IL-17A signature increases after treatment with TNF blockade [25, 43]. Similarly, we will use the RNA sequencing data to look at immune subset-specific differential gene expression from Th17-high, anti-IL-17A responders and refractory patients and TH17-low anti-TNF responders and refractory patients. Genes identified will be validated in the whole blood RNA sequencing data-set and we will use network and pathway analysis to identify key nodes of refractory disease which can be validated in future mechanistic studies.

11.3. Sample Size Determination

This study has been powered to test for a biomarker-treatment interaction in response as defined by achievement of the MDA criteria at 24 weeks. Based on RCT and registry data for both drugs [10 24 25], we expect similar non-biomarker stratified MDA response rates in each treatment arm in the RCT and estimate the MDA response rate overall to be ~50%.

Original Sample Size Calculation

The original required sample size for OPTIMISE at inception was 424 participants. This was based on the ability to detect a biomarker-treatment relative interaction effect of 0.2, with 98% power, which is derived from the assumption that the proportion of MDA responders is 60% and 40% for participants with low/high Th17 treated with TNFi, and 40% and 60% for participants with low/high Th17 treated with IL-17Ai. We defined 'interaction' as a difference in the MDA-response rate according to whether TH17 level is either *high* or *low*. This infers that we assume that the proportion of MDA responders (the trial primary outcome) is 60% and 40% for participants with low/high TH17 treated with TNFi, and 40% and 60% for participants with low/high TH17 treated with IL-17Ai. This analysis requires the TH17 levels recorded in the trial to be converted from their original allele frequency into a dichotomous variable split around the median (which creates a 50:50 split of participants into either 'high TH17' (those greater than the median level) or 'low TH17' (those lower than the median TH17 level)).

A recently published open-label head to head study of a TNF inhibitor versus an IL-17A inhibitor reported a slightly lower response rate (48 vs 35%)[26] than we have assumed. We expect a higher achievement of MDA in our study as our patients will have lower baseline active joint counts and psoriasis severity compared to those recruited into this large pharmaceutical sponsored RCT. The original calculation was powered at 98% as this gave sufficient power of >80% even if the response rates were lower than anticipated.

Revised Sample Size Calculation

Splitting TH17 level into a dichotomous variable, while simple to interpret, causes information loss, and therefore reduces available power, increasing the required sample size. A revised sample size instead using TH17 level in the analysis as a continuous outcome, and assuming the same relative interaction effect of 0.2, and the same type-I error rate of 0.05, and a reduced power of 90% was produced to decrease the required sample size in the event that recruitment became challenging. This calculation assumes a 'main effect' of treatment response (the difference in response between treatment arms

distinct from the interaction effect) of 0.2 (as in the original calculation), and no direct correlation between TH17 level and response after including the interaction effect. Under these assumptions, a simulated sample size produced in R (Version 4.2.1), and using the {InteractionPoweR} package using 10,000 simulated iterations produced a required sample size of 240 participants (120 per group), which, including a loss-to-follow-up of 10%, translates to a required recruitment of 134 participants per group (268 in total).

A difference of 20% in rates of achievement of MDA has been chosen as a level that is highly likely to change clinical practice. The Tight Control of PsA (TICOPA) study looking at a treat-to-target approach also used the same predicted difference of 20% although with a lower level of response defined by ACR20. The primary outcome of this study was achieved by 62% of the tight control patients vs 44% of those in standard care. As a result of this study, the first recommendation of the EULAR PsA treatment recommendations is that patients should be treated using a treat-to-target approach and there have been subsequent specific treat-to-target recommendations based on this data alone. We feel that a difference of 20% has the ability to strongly inform changes in practice, particularly as the outcome used in this study is a stringent response equivalent to an optimal treatment goal.

11.4. Analysis populations

All participants will be included as randomised (intention to treat) analysis.

11.5. Decision points

No formal comparative interim analysis will be undertaken but an independent Data and Safety Monitoring Committee will review accruing data, conduct and safety and will undertake a blinded review of the assumptions used in the sample size calculation (e.g. response rates) approximately half-way through the study.

11.6. Stopping rules

There are no planned stopping rules.

11.7. The Level of Statistical Significance

The level of significance to be used is 0.05.

11.8. Procedure for Accounting for Missing, Unused, and Spurious Data.

It is intended that analysis will be on complete cases, but the nature and pattern of missingness will be carefully considered and documented, in particular as to whether the data can be treated as missing at random. If appropriate, missing data will be imputed using various assumptions for missing data mechanisms to check the robustness of the primary analysis. Reasons for ineligibility, non-compliance, withdrawal or other protocol violations will be documented.

11.9. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any deviation(s) from the original statistical plan will be described and justified in the protocol and/or in and updated statistical analysis plan and/or the final report, depending on the timing of the changes.

11.10. Health Economics Analysis

Not applicable.

12. DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the Data Management Plan.

12.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). For this study the following data are expected to be captured directly on the CRFs thus are considered source documents:

- Patient reported questionnaires

Source data will also be generated through the analysis of the blood samples for study purposes.

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent form, the participant will be referred to by the study participant number/code and initials, not by name.

12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

12.3. Data Recording and Record Keeping

The results of the composite clinical outcome measures will be recorded in the patients' medical notes and will be extracted by a study investigator and entered into an eCRF. The routine clinical blood samples will be processed at the clinical site laboratory and the results entered into the eCRF by the participating site.

The participants will be identified by a unique trial specific number in any database. The name and any other identifying detail will NOT be included in any trial data electronic file.

All paper documents containing personal data (e.g. informed consent forms) will be stored securely and only accessible by study staff and authorised personnel. The study investigator is responsible for keeping

these documents securely to ensure that in case of an emergency, participants can be identified and contacted. The code list will be kept for the archive period as specified in section 20.

All study data will be stored for five years after the end of the study. To meet HTA traceability requirements consent forms for those participants who provide consent to the long term storage and future use of samples will be retained until the sample is depleted or destroyed.

During and/or after the end of the study a de-identified study dataset will be created and stored for as long as it is useful, and may be shared with the NIHR (funder) and other researchers upon request and/or uploaded into a research data repository. Sharing and storage of this data will continue for as long as this data is useful.

A data management plan for the study will be written in line with OCTRU SOP requirements.

13. QUALITY ASSURANCE PROCEDURES

This study will be coordinated by the UKCRC registered Oxford Clinical Trials Research Unit (OCTRU) at the University of Oxford. The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

13.1. Risk assessment

A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities.

13.2. Study monitoring

Regular monitoring will be performed according to the study specific Monitoring Plan to verify that the clinical study is conducted, and data are generated, documented and reported in compliance with the protocol, the principles of GCP and the applicable regulatory requirements.

13.3. Study Committees

13.3.1. Trial Management Group

The Trial Management Group (TMG) will consist of the core study team, relevant CTU members, the Chief Investigator and grant co-applicants.

The TMG will be responsible for running the study and will meet, usually on a monthly basis, to report on progress and ensure milestones are met. The TMG will be responsible for the close monitoring of recruitment and the decision to increase the number of participating sites, with a formal review of this occurring 6 months after the start of recruitment. A Charter or Terms of Reference will be put in place according to OCTRU SOPs.

13.3.2. Data and Safety Monitoring Committee

The Data and Safety Monitoring Committee (DSMC) will monitor accruing data, study conduct and safety of the participants. The DSMC will also undertake a blinded interim review of the data to ensure that the

assumed response rates overall are as expected. The DSMC will meet at least annually during the recruitment period.

A DSMC Charter will describes the membership, remit and responsibilities of this committee.

13.3.3. Trial Steering Committee

The Trial Steering Committee (TSC) will be comprised of independent clinicians, statisticians, health service researchers, and lay patient representatives. The TSC will monitor the study's progress and safety and will provide independent advice.

The TSC will meet 6 months after the start of recruitment then at least every 12 months subsequent to that during the recruitment period.

A TSC Charter will describe the membership, remit and responsibilities of this committee.

14. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from the principles of Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented and reported to the Coordinating Trial Office.

OCTRU standard operating procedures will be in place describing the procedure for identifying non-compliances, escalation to the trial management team and assessment of whether a non-compliance /deviation may be a potential Serious Breach.

15. SERIOUS BREACHES

A "serious breach" is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

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

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

Any site staff who become aware of a potential serious breach must report this to the coordinating trial office as soon as possible. The trial team at the coordinating trial office will then liaise as the Sponsor and CI as required.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Compliance

The trial will be conducted in compliance with the approved protocol and standard operating procedures (SOPs), the Declaration of Helsinki, the principles of Good Clinical Practice (GCP), the UK Data Protection Act and all other applicable regulatory and governance frameworks including the UK policy framework for health and social care research.

16.2. Approvals

Following Sponsor approval the protocol, informed consent form, participant information sheet will be submitted to an appropriate Research Ethics Committee (REC), and HRA (where required) and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.3. Other Ethical Considerations

A small number of the questions in the participant questionnaires may be upsetting to some participants. As participants will be completing the questionnaires during their outpatient appointments their clinical and/or research team will be present and able to support them should this occur. If anything of clinical significance is identified, the clinical team will be notified.

16.4. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

16.5. Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database.

Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

16.6. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), with the exception of the CRF and blood samples, where participant initials may be added. All documents will be stored securely and only accessible by

study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

16.7. Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

17. FINANCE AND INSURANCE

17.1. Funding

This trial is supported by a grant from the NIHR, Efficacy and Mechanism Evaluation (EME) Committee (ref NIHR129023). The sub- study with synovial biopsy is supported by Oxford Biomedical Research Centre & Glasgow Core Funds.

17.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

17.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

18. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by NIHR. In-keeping with the contractual arrangements in place, publications including abstracts will be submitted to NIHR prior to submission for publication. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

A lay summary of the results will be published on a publicly accessible trial website.

19. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

20. ARCHIVING

Archiving will be carried out in line with OCTRU SOPs. Study sites will be responsible for the archiving of site documents and records and source data. All study records must be archived for 5 years after the

end of the trial. Permission to destroyed archived records must be received from the Sponsor prior to any destruction.

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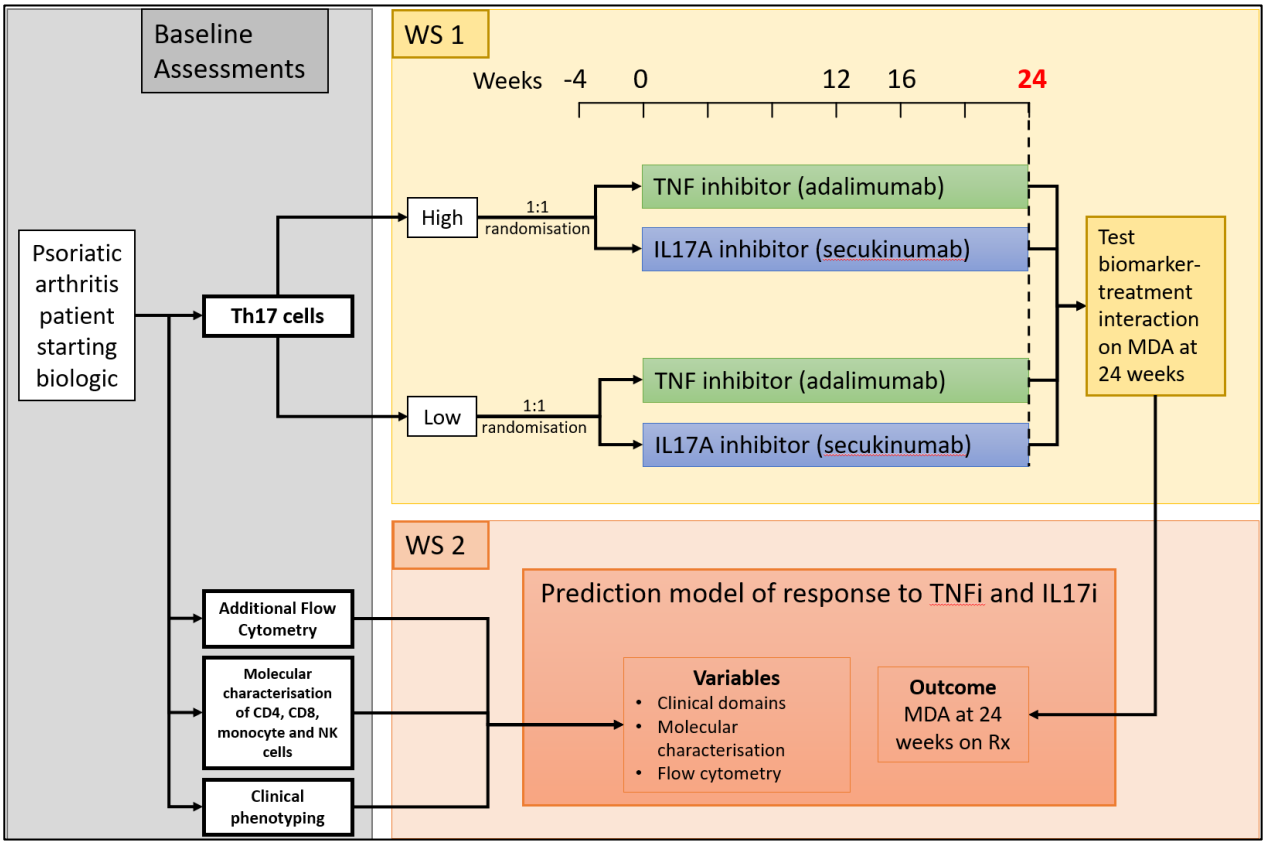
22. APPENDIX A: STUDY FLOW CHART



23. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

Procedures	Visits & timing						
	Screening Week -6 - 0	**Randomisation Week -6 - 0 (no visit)**	**Baseline Day 0 (remote visit)[1]**	**Week 4[2] (+/- 1 week)**	**Week 12 (TNFi only) (+/- 2 weeks)**	**Week 16 (IL-17Ai only) (+/- 2 weeks)**	**Week 24 (+/- 2 weeks)**
Informed consent	X						
Record demographics	X						
Medical history	X				X	X	X
Concomitant medication check	X				X	X	X
Eligibility assessment	X						
Composite clinical outcome measures	X				X	X	X
Anthropometrics	X						
Blood sample	X			X[2]			X[2]
Synovial fluid and synovial tissue samples	X[3]						X[3]
Randomisation		X					
First dose of study treatment			X				
Adverse event assessments					X	X	X

[1] Baseline is expected to occur 3-4 weeks after randomisation due to the time needed for the provision of treatment to participants via standard NHS procedures. It is recognised that the anticipated time to deliver the drug might be delayed due to pressure on NHS pharmacies. If > 4 weeks delay, this will not be considered a protocol deviation.

[2] Participants at main hub sites only (Oxford, Glasgow & London) (~100 in total).

[3] Optional sub study only at Oxford & Glasgow sites.

24. APPENDIX C: ULTRASOUND GUIDED SYNOVIAL BIOPSY STANDARD OPERATING PROCEDURE

Equipment

- Quick-Core biopsy needles 14 G /16 G all with 20mm throw size, with at least a 6cm co-axial needle.
- Sterile table cover
- Sterile Fenestrated drape
- Sterile Ultrasound sheath
- Sterile gown and gloves
- Face mask / hair cover
- Sterile swabs x 3
- Sterile bowls x 2
- Sodium chloride 50ml
- Chlorhexidine and Hydrex surgical scrub for skin prep
- Wound dressing pack for skin prep
- 2.5ml / 5ml / 10mls syringes
- Needles x2 21G short needles from drawing up drugs, x1 21G long needle to give lidocaine.
- Scalpel
- Scissors
- 1 % Lidocaine (max 4.5mg/kg)
- Butterfly stitches
- Sterile Dressing
- Sample container for processing
- Sample shipment box including sample packs bloods and synovium.
- Flat tip forceps for transferring samples

Personnel

- Ultrasonographer performing the biopsy
- Technician/nurse/clinical fellow for tissue processing

Joint Identification

The most appropriate joint for synovial biopsy is selected by the operator.

Biopsy procedures

The biopsy procedures outline below are based on the most frequent joints used for synovial tissue retrieval.

Knee

Patient Orientation

The patient should be placed supine on a bed. The patient may remain recumbent at 45 degrees or preferably lie flat during the procedure, with the knee slightly flexed (25-30 degrees) to improve imaging of the supra-patella pouch.

Preparation

- The operator should now evaluate the equipment tray including biopsy needle and commence personal preparations for the procedure (hand washing, gloves, face mask, hair net, sterile gown).
- With the patient suitably placed on the bed, suitable absorbent pads should be placed under the knee. The skin should be prepped with appropriate sterilization. A wide field should be sterilized in excess of the immediate area of interest, approx. mid-thigh to mid-calf both anteriorly and posteriorly.
- Sterile drape should be positioned on the knee leaving sufficient space for access to the supra-patella pouch and placement of the US probe for the purposes of imaging.
- 10mls of 1% lidocaine should be aspirated into a syringe containing 10mls of normal saline. This mixed solution will be introduced into the synovial space later.
- US examination of the lateral aspect of the knee should indicate a suitable area for needle insertion distal to the vastus lateralis muscle insertion into the patella.
  The US probe should be placed within the sterile sheath. US gel should be placed first upon the probes foot-print and slowly lowered into the sheath. The upper end of the sheath should be secured with a sterile tie or elastic band usually provided with the sheath.
- Note: Operator uses double gloving for preparation

Procedure

- Inject up to 10mls of 1% lidocaine into the subcutaneous and deep tissue at the predetermined point of insertion as identified by the initial US scan. Leave a minimum of 1-2mins for effect.
- Using a 18G needle and under US guidance, aspirate as much fluid as possible from the supra-patella pouch. Disconnect the syringe leaving the needle in situ. Now introduce up to 5mls 1% lidocaine) then remove needle. The lidocaine can be mixed with 10mls of normal Saline in order to enable a better image to be acquired during the procedure and facilitate clear identification of synovial tissue. Smaller amount of normal saline and lidocaine may be used depending on the size of the patient and volume of synovial fluid present.
- The quick core biopsy needle should be primed before its introduction to the synovial space.
- Introduction of the biopsy needle into the supra-patella pouch can now be performed under ultrasound guidance.
- The needle should be extended and the throw identified on the US images. The throw of the needle should be placed against the surface of the synovium to maximize the opportunity for capturing the lining layer. Gentle pressure should be placed on the needle to oppose the throw and synovium. NOTE: if the tip of the extended needle is abutting a bony surface, backwards movement of the needle will occur at this stage with poor retrieval of tissue.
- After sufficient numbers of specimens have been harvested, any remaining fluid should be aspirated.

Wrist

Patient Orientation

The patient should be placed supine on a bed. The patient may remain recumbent at 45 degrees, with the hand placed on a table next to the bed. Care should be taken not to elevate the hand or abduct the shoulder significantly as this will cause patient discomfort during the procedure. The hand should be place with the palm downwards.

Preparation

- Patient suitably placed on bed, suitable absorbent pads should be placed under the wrist.
- Wash hands, gown, apply mask, hair cover per normal sterile preparation.
- The skin should be prepped with sterilization. A wide field should be sterilized in excess of the immediate area of interest, approx. Hand to mid-forearm (dorsal and ventral aspects).
- Sterile drape should be positioned on the wrist on the table.
- The wrist may be placed in slight palmar flexion to improve access and identification of the synovial recesses. A piece of sterile gauze may be placed under the wrist to elevate the joint to facilitate better access and manoeuvrability when performing the biopsy procedure.
- The US probe should be placed within the sterile sheath. US gel should be placed first upon the probes foot-print and slowly lowered into the sheath.
- The upper end of the sheath should be secured with a sterile tie or elastic band usually provided with the sheath.
- 10mls of 1% lidocaine should be aspirated into a syringe.
- US examination of the wrist should be performed prior to the biopsy to identify suitable approach for biopsy.

Procedure

- Inject up to 5ml of 1% lidocaine into the subcutaneous tissue up to the extensor retinaculum. Leave a minimum of 1- 2mins for effect.
- Using a 21G needle and under US guidance, aspirate any fluid. This is an opportunity to plan for the biopsy needle insertion. Now introduce up to 1ml of 1% lidocaine. This will enable a better image to be acquired during the procedure and facilitate clear identification of synovial tissue.
- The quick core biopsy needle should be primed before its introduction to the synovial space.
- Introduction of the biopsy needle into the wrist can now be performed under ultrasound guidance.
- The needle should be extended and the throw identified on the US images. The throw of the needle should be placed against the surface of the synovium to maximize the opportunity for capturing the lining layer. Gentle pressure should be placed on the needle to oppose the throw and synovium. NOTE: if the tip of the extended needle is abutting a bony surface, backwards movement of the needle will occur at this stage with poor retrieval of tissue.
- After sufficient numbers of specimens have been harvested, any remaining fluid should be aspirated.

MCP Joint

Patient Orientation

The patient should be placed supine on a bed. The patient may remain recumbent at 45 degrees, with the hand placed on a table next to the bed. Care should be taken not to elevate the hand or abduct the shoulder significantly as this will cause patient discomfort during the procedure. The hand should be place with the palm downwards.

Preparation

- With the patient suitably placed on the bed, suitable absorbent pads should be placed under the wrist.
- The preparation for an MCP joint biopsy is identical to the wrist biopsy detailed above.
- US examination of the MCP joint to be biopsied should identify synovial thickening and plan the path of needle entry into the joint space. Typically the recess behind the metacarpal head gives access to adequate synovial tissue and is relatively easy to target.
- The digital vascular supply should be identified and a path of entry to the synovium planned accordingly.

Procedure

- Inject up to 5 mls of 1% lidocaine into the subcutaneous tissue up to the capsule. Leave a minimum of 1-2 mins for effect.
- Using a 23G needle and under US guidance, aspirate any fluid. This is an opportunity to plan for the biopsy needle insertion. Now introduce up to 1 ml of 1% lidocaine. This will enable a better image to be acquired during the procedure and facilitate clear identification of synovial tissue.
- The quick core biopsy needle should be primed before its introduction to the synovial space.
- Introduction of the biopsy needle into the MCP joint can now be performed under ultrasound guidance. This is best achieved by imaging the needle in the long axis. The path of the needle will be dictated by the previous guided injection of local anaesthetic. US examination of the MCP joint should be performed prior to the biopsy to identify suitable approach for biopsy.
- The needle should be extended and the throw identified on the US images. The throw of the needle should be placed against the surface of the synovium to maximise the opportunity for capturing the lining layer. Gentle pressure should be placed on the needle to oppose the throw and synovium. NOTE: if the tip of the extended needle is abutting a bony surface, backwards movement of the needle will occur at this stage with poor retrieval of tissue.

Post-Procedure Care

- Butterfly stitches and a small dressing are used to cover the wound.

25. APPENDIX D: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
n/a	2.0	15Feb2021	Anne Francis	Changes in response to REC & HRA review. Typographical corrections.
1	3.0	03Aug2021	Anne Francis	Addition to exclusion criteria of those unwilling to follow contraceptive advice. Addition of section 10.3 Contraception & Pregnancy. Update of section 12.3 to include clause on data sharing.
			Laura Coates, Alexander Ooms	Addition of 2 new secondary objectives that had been omitted from original protocol in error.
			Mimi Bogale	Update Planned Study Period start date to match start of planned recruitment period. Addition of visit windows for the follow-up visits week 4, week12/16 and week 24 to Appendix B (Schedule of study procedures). Update on section 9.4 to clarify randomisation will be performed centrally by CTU staff.
			Mimi Bogale	Administrative changes: addition of logo's, update to abbreviation list, addition of public title and registration number, correction of typographical errors on section 9.9
2	4.0	03May2022	Mimi Bogale	Administrative changes: change in Senior Statistician, Sponsor name change, addition of telephone number for Trial Manager, and correction of typographical error on abbreviation list and section 7 Changes in Planned Study and Recruitment Period. Inclusion criteria 4 updated to include eligibility for biologics treatment under NICE/SMC or local guidelines. Update to the Recruitment section to include Patient Identification Centres as a means to identify potential participants. Addition of options for where samples for RNA sequencing will be process and sequenced.

			Alexander Ooms	Change in section 9.2 to cover where consent form is being sent to Time window for sample transfer to hub sites as specified in the OPTIMISE Sample Handling Manual. Changes in the Objectives &Outcome measures table: moved a secondary outcome to exploratory, removed reference to 4-week data in two secondary outcomes as this is not being captured. Changes also made in Section 3 Synopsis table.
3	5.0	05Jul2022	Mimi Bogale	Correction of typographical error on section 8.2 (inclusion criteria 4) and section 9.2 (informed consent). Addition of a footnote on appendix B to clarify the delay in drug delivery by NHS pharmacies.
4	6.0	29Mar2023	Mimi Bogale Laura Coates Matthew Parkes	Changes following sample size reduction Key contacts table updated following change in trial statistician and sponsor email address. Synopsis, Objectives and outcome measures table updated following changes to primary analysis. Section 11.3 updated following revised sample size.
5	7.0	25May2023	Mimi Bogale	Administrative : change in Senior statistician and correction of typographical error on page 2. Extension of recruitment end date.
6	8.0	07Nov2023	Mimi Bogale	Changes to Planned Study and Recruitment Period. Administrative change: OPTIMISE Trial Manager telephone number update.
7	9.0	05Aug2024	Laura Coates Mimi Bogale	Optional sub study with collection of synovial fluid and tissue at baseline and week 24 visits added (only available at some study sites). Change to Exclusion criteria to allow Apremilast treated patients in the study Appendix B: Correction of typographical error.

				Sample size amended from '240' to '268' to include 10% drop-out. Relevant section on Funding updated to reflect funding arrangement for the sub-study.
			Aurelie Najim & Shing Law	Appendix C added for optional sub study with biopsy samples
8	10.0	04Nov2025	Laura Coates, Carl Goodyear, Anne Francis, & Sofia Massa	Clarification and update of plans for laboratory analysis given recent data in the field.
			Annabel Morley	Minor amendments to typographical or grammatical errors.

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee and HRA (where required).