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Optimising Psoriatic Arthritis Therapy with Immunological Methods to Increase Standard Evaluation: The protocol of an open-label multi-centre, parallel-group, two arm randomised controlled study evaluation precision medicine approach in the treatment of psoriatic arthritis.

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Title

Optimising Psoriatic Arthritis Therapy with Immunological Methods to Increase Standard Evaluation: The protocol of an open-label multi-centre, parallel-group, two arm randomised controlled study evaluation precision medicine approach in the treatment of psoriatic arthritis.

Short title

The OPTIMISE Study

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Abstract – 292/300 words

Introduction – Psoriatic arthritis (PsA) affects around 150,000 people in the UK of whom around 50% require treatment with biologics. The most used biologics for PsA target tumour necrosis factor (TNF) or interleukin-17A (IL-17A). About 50% of patients respond to each but it is not currently possible to predict response for individual patients, necessitating sequential treatment steps. A recent proof of concept study in PsA suggested that using peripheral immunophenotype to choose therapy could improve time to treatment response.

This study will test the hypothesis, within an open-label parallel-group biomarker-stratified multi-centre randomised controlled trial, that the baseline proportion of CD4+ T cells with an activated Type 17 immunophenotype (Th17 levels) predicts response to IL-17A or TNF inhibitors in PsA. Additional analyses will identify if the model can be refined by combining additional clinical and immunophenotypic factors. Statistical modelling will be used to predict the likely effectiveness of these approaches compared with standard care.

Methods and analysis: Patients with PsA eligible to start their first biologic as part of standard care are recruited and baseline blood tests taken for immunophenotyping. Participants are stratified equally by Th17 levels and randomised 1:1 to receive either TNF (adalimumab) or IL-17A (secukinumab) inhibitors. The primary analysis will establish the interaction between baseline immunophenotype and treatment on the primary outcome (achievement of minimal disease activity criteria at week 24). In secondary analysis, modelling will identify if this prediction model can be optimised further by incorporating clinical phenotypes and additional immunophenotyping techniques.

Ethics and dissemination – Ethical approval for the study was granted by the North West Preston Research Ethics Committee (ref 21/NW/0016)

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Strengths and limitations (5 bullet points related to methods)

- The OPTIMISE study is the first powered randomised controlled trial investigating a precision medicine approach to biologic selection in PsA.
- Broad eligibility criteria, in keeping with current UK treatment recommendations, increase the generalisability of the trial results to clinical practice.
- Both participants and clinicians are blinded to the immunophenotyping data minimising bias in the analysis.
- Detailed immunophenotyping using multiple laboratory approaches will maximise the chances of identifying key predictive markers for response.
- Of note, immunophenotyping requires considerable cell processing and is not yet optimised for routine diagnostic use.

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Introduction

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 levels reported for 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 an empiric 'step up' 'trial-and-error' approach using different conventional disease-modifying anti-rheumatic drugs (DMARDs) followed by biologic DMARDs if patients do not respond [1, 6]. Approximately 50% of patients with PsA will require biologic therapy [7] with four key mode of action drugs available. The most commonly used biologic treatments for PsA target one of two main immunological pathways: tumour necrosis factor (TNF), or interleukin (IL) 17. Arthritis response rates to both drugs are similar, with 60-70% of patients achieving at least a partial response. In clinical practice, biologic therapies need to be used for a minimum of 12-16 weeks before response can be evaluated [1, 6], with assessment of achievement of treatment target later [8]. For many patients this means protracted administration of a therapy that may never work, in addition to financial and clinical NHS costs.

Two head-to-head parallel-group randomised studies comparing TNF and IL-17A inhibitors in PsA have been performed showing no significant differences in peripheral arthritis outcomes.[9, 10] Currently, clinicians select therapies based on a limited clinical phenotype, such as differentiation in skin psoriasis, comorbidities, personal experience and cost. Despite similar responses at a group level, we know that some people who fail to respond to a first biologic will have a good response when they switch to a drug with a different mechanism of action [11] suggesting that disease immunopathogenesis varies between individuals. However, treatment in these studies was randomly allocated, with only one previous study in PsA with any precision medicine element.

This study in Japan evaluated the use of baseline CD4+ T cell immunophenotype characteristics to inform selection of biologic therapy [12]. They defined four groups based on predetermined cut-offs for high and low levels of Th1 and Th17 cells, based on quartiles in healthy controls. Sixty-four PsA patients starting biologic therapy were randomly divided into a standard care group (IL-12/23, IL-17A or TNF inhibitors) and a precision medicine group (n=26) in which the choice of therapy was based on the peripheral blood lymphocyte analysis. The precision medicine group had significantly higher rates of ACR20 response and low disease activity, although other measures, including psoriasis responses, were not significantly different. The study was not powered to compare the treatment groups and did

not include a pre-specified primary outcome. However, the results are promising, and the study urgently requires confirmation.

A more rational approach to treatment selection has the potential to make a substantial contribution to patient care by increasing the chance of identifying the biologically rational treatment for the patient. Thus, the primary aim of the OPTIMISE (Optimising Psoriatic arthritis Therapy with Immunological Methods to Increase Standard Evaluation) study is to identify a peripheral immunophenotype that can predict response to biological therapy in PsA and facilitate a stratified approach to treatment.

Objectives

Our primary objective is to establish the interaction between baseline immunophenotype (proportion of CD4+ T cells with an activated Th17 cell profile) and treatment (IL-17A or TNF inhibitor therapy) on the proportion of PsA patients achieving the minimal disease activity (MDA) criteria at week 24 (primary outcome).

Our secondary objectives will compare responses to both medications dependent on intracellular IL-17 levels and immune-subset transcriptomic signatures to see if additional immunological markers can predict response to either drug. Treatment response from a patient's perspective is assessed through patient reported outcome measures. We will also explore changes in the immunological markers with treatment and assess if these correlate with clinical response. These objectives are all summarised in Table 1.

Table 1 – primary, secondary and exploratory objectives for the OPTIMISE trial

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objective To test whether the clinical response to TNF and IL-17A inhibitor therapy in participants with PsA differs according to the level of baseline activated Th17 cells.	Clinical response as measured by the minimal disease activity (MDA) criteria	Immunophenotype data at baseline and clinical response at week 24.

Secondary Objectives To test whether the clinical response to TNF and IL-17A inhibitor therapy in participants with PsA differs according to intracellular IL-17 levels.	Clinical response as measured by the minimal disease activity (MDA) criteria	Immunophenotype data at baseline and clinical response at week 12/16 and week 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 week 24.
To explore if the immune subset-specific transcriptomic signature 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 scores and in overall disease as measured by the PsA disease activity score (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 the immune subset-specific transcriptomic signature to identify a limited number to of transcriptomic biomarkers that can be validated in whole blood.	Cell specific transcriptomic data and whole blood transcriptomes	Immunophenotype data at baseline and week 24.
To use the immune subset-specific transcriptomic signature to define the pathways driving biologic-refractory disease.	Cell specific transcriptomic data and whole blood transcriptomes	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 with additional immunophenotypic (intracellular CD4 Th17 frequency, CD8 Tc17 frequency, MAIT cell frequency, immune transcriptomic signature) factors to develop a predictive model for response to IL-17A and/or TNF inhibitor therapy in PsA.	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.
To test whether the clinical response to TNF and IL-17A inhibitor therapy in participants	Clinical response as measured by the minimal disease activity (MDA) criteria	Immunophenotype data at baseline and clinical response at week 12/16.

with PsA differs according to the level of baseline activated Th17 cells.		
To explore if the change or absolute levels of activated Th17 surface and intracellular signature or the transcriptomics 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.

Our exploratory objective is to use machine learning and predictive modelling to combine baseline clinical phenotypic markers such as disease duration and clinical expression of disease, with additional immunophenotypic (intracellular cytokine staining to determine IL-17A+CD4+ (Th17) or IL-17A+CD8+ (Tc17) frequencies, MAIT cell frequency, immune transcriptomic signature) factors to develop an optimal predictive model for individual responses to IL-17A and/or TNF inhibitor therapy in PsA.

Our exploratory mechanistic objectives are:

- To understand if the activated Th17 surface and intracellular signature (and possibly also other IL-17 signatures) resolve after treatment with IL-17A inhibitors and how these are altered after TNF inhibitor therapy with additional focus on the polyfunctional cells producing multiple cytokines.
- To understand if changes in the activated Th17 surface and intracellular signature (and possibly other IL-17 signatures) differ in treatment responders and non-responders.
- To explore if immune subset-specific transcriptomic signatures can be used to predict efficacy of IL-17A and TNF inhibitor therapies either alone or in combination with the activated surface and intracellular Th17 signatures.
- To use the identified transcriptomic signature to identify a limited number of transcriptomic biomarkers that can be validated in whole blood.
- To use the immune subset-specific transcriptomic signature to define the pathways driving biologic-refractory disease.
- To establish a biobank of samples at the end of this analysis to allow future investigation of novel scientific techniques and biomarkers within this population (with future separate funding).

Methods and analysis

Study design

The OPTIMISE study is an open-label parallel-group biomarker-stratified multi-centre randomised controlled trial of adults with PsA where participants are randomised to either TNF or IL-17A inhibitors, testing whether this or other immunological markers can predict achievement of the MDA criteria after 24 weeks on therapy. This paper describes v7.0 (dated 24May2023) of the protocol. Changes in the protocol since v1.0 include

- Initial modification in response to research ethics committee review
- Addition of exclusion criteria for those unwilling to follow contraceptive advice
- Inclusion of eligibility for those who have failed 1 conventional DMARD but are eligible for treatment under local guidelines
- Changes to study recruitment dates and inclusion of patient identification centres (PICs)
- Changes to sample size (as outlined below)

Selection of Population

The population included are adults (≥18 years old) with PsA fulfilling the CASPAR criteria who are due to start biological therapy for their PsA according to established UK eligibility criteria. This typically requires patients to have failed to respond to ≥2 conventional DMARDs and to have active disease demonstrated by ≥3 tender/swollen joints. Patients with previous exposure to biological therapies or those who have contraindications to either drug are excluded from participation. Full inclusion and exclusion criteria are shown in Table 2.

Table 2 – Inclusion and exclusion criteria for the OPTIMISE trial

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 conventional DMARDs and ≥3 tender AND ≥3 swollen joints).
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
- 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.

Randomisation, blinding and allocation concealment

Prior to randomisation, we record the therapy that was planned by the physician if they had not been recruited to the trial.

Eligible and consented patients are randomised centrally by clinical trial unit staff using the bespoke computerised trial unit specific randomisation system. Patients are randomised in a 1:1 allocation ratio to either TNF (adalimumab) or IL-17A (secukinumab) inhibitor. The randomisation uses a minimisation algorithm to ensure balanced allocation across the treatment groups, stratified by activated Th17 proportion (≤/>1.58%), psoriasis severity (psoriasis area and severity index [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 to ensure the unpredictability of treatment allocation. There is no blinding of therapy allocation for patients or clinicians so no allocation code or code-breaking procedure is required, however the baseline immunophenotype data will be blinded from all participants and clinical study site personnel,

while laboratory staff will be blinded to the allocated therapy. Unblinding should not be required during the study as it will not have clinical relevance to treatment decisions.

Interventions, patient follow-up, visits and trial procedures

Following consent, patients undergo a baseline clinical assessment and blood is taken for immunophenotyping. Fresh peripheral blood samples (50mls) are couriered to one of the three laboratory hub sites (Oxford, Glasgow, London) for processing within 6 hours and are then cryopreserved for mechanistic cellular work (peripheral blood mononuclear cells [PBMCs]) or whole blood RNA sequencing). Our preliminary analysis shows that peripheral Th17 surface and intracellular signatures at 6 hours are comparable to freshly isolated samples. The measurement of the biomarker will be processed simultaneously with local processing of standard clinical safety screening for biological therapies (e.g. hepatitis/TB screening), avoiding delay to patients' treatment.

Analysis will be performed on cryopreserved samples rather than fresh samples to allow standardisation across centres, avoid delays to samples arriving late in the day and avoid issues with temporary unavailability of essential laboratory machinery such as flow cytometers. In the primary laboratory analysis, the samples will undergo ten colour flow cytometry. In the first instance, activated Th17 frequencies will be identified based on CCR6+ and CXCR3- expression on CD3+CD4+CD8- T cells and co-expression of known T cell activation markers CD38 and HLA-DR, as described in the Miyagawa study[12]. The proportion of activated Th17 cells will be included in the randomisation process to ensure equal stratification across the treatment arms.

The TNF inhibitor used in the study is adalimumab (any brand, including biosimilars) and is given at the usual licensed dose of 40 mg by subcutaneous injection every 2 weeks, with no loading doses. The IL-17A inhibitor used is secukinumab, brand name Cosentyx, and is given at the usual licensed dose which varies based on the level of baseline skin psoriasis. The usual recommended dose as a first line biologic in PsA is 150mg by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4 followed by a monthly maintenance dose. For patients with concomitant moderate to severe plaque psoriasis, the recommended dose is 300mg by subcutaneous injection at the same timepoints. This study therefore follows 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 from 150mg to 300mg in the case of a partial response to treatment as per the licence is permitted. Both drugs are provided from usual NHS stock and are self-administered by the patients following standard initial training, as per usual clinical practice.

The study involvement for each participant is 24 weeks plus the screening period (typically 4-8 weeks). Drug treatment is started at baseline and continued for the 24 weeks with study 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. Patients recruited at the hub sites are also asked to attend at week 4 for a research blood sample to be taken. After the 24-week study treatment period, participants who have responded well to treatment can continue on treatment following the end of the study period or switch to another treatment in line with usual NHS practice. Any patient discontinuing treatment for clinical reasons will be encouraged to attend for study visits and any treatment changes will be documented.

Sample size

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 [13-15], 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%.

Initially, the analysis planned to detect a biomarker-treatment relative interaction effect of 0.2, with >90% power and 5% type I error, using a difference in the MDA-response rate according to whether the proportion of activated Th17 cells 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 TNF inhibitors, and 40% and 60% for participants with low/high Th17 treated with IL-17A inhibitors This resulted in an original sample size of 424 participants.

However, this analysis would have converted the Th17 levels recorded in the trial into a dichotomous variable split around the median, creating two subgroups: 'high Th17' and 'low Th17'. Applying such a dichotomy causes information loss and reduces available power. Therefore, during recruitment an amendment was proposed and approved to use the proportion of activated Th17 cells in the analysis as a continuous outcome, whilst assuming the same relative interaction effect of 0.2, type I error rate of 0.05 and 90% power. This resulted in a reduction in the required sample size to 240 participants without a loss of power. This assumes a 'main effect' of treatment response (the difference in response between treatment arms distinct from the interaction effect) of 0.2, and no direct correlation between Th17 level and response after including the interaction effect.

Recruitment

Enrolment occurs within rheumatology outpatient clinics at participating UK hospital sites. Potential participants are approached by their clinical team after the decision has been made to start biologic therapy as part of standard clinical care and guidance. Written consent is obtained from potential trial

participants by the principal investigator or a designated member of study staff. With 17 sites, it is estimated that recruitment will complete in 36 months. The trial opened for recruitment in January 2022 and the estimated completion date is December 2024.

Outcomes

The primary outcome will be treatment response as measured by the proportion of patients achieving the MDA criteria [16] at 24 weeks (see Table 3).

Table 3 – Minimal disease activity (MDA) criteria

Patients are classified as being in MDA when they achieve any 5 or more of the following 7 criteria
Tender joint count ≤ 1
Swollen joint count ≤ 1
Psoriasis area and severity index ≤ 1
Enthesitis score ≤ 1
Patient global visual analogue scale of disease activity ≤ 20mm
Patient visual analogue scale of pain ≤ 15mm
Health assessment questionnaire score ≤ 0.5

Individual secondary outcome measures covering all of the new 2016 Outcome Measures in Rheumatology Clinical Trials (OMERACT) core and strongly recommended domains for PsA studies [17] are collected at all timepoints, with the exception of radiographic damage which is inappropriate in a short duration, active comparator study. The secondary outcome measures are listed in Table 4. The electronic case report form (eCRF) system REDCap is being used to collect the data.

Table 4 – secondary outcome measures for the OPTIMISE trial

Musculoskeletal disease activity	Physician global visual analogue scale (VAS), 68 tender joint count (TJC) and 66 swollen joint count (SJC) [19], Leeds [20] and Spondyloarthritis Research Consortium of Canada (SPARCC) [21] enthesitis indexes, dactylitis count [22],
Psoriasis disease activity	PASI [23] and nail disease VAS
Pain	Patient pain VAS [19]
Global	Global disease activity VAS [24]
Physical function	HAQ [25]
Health related quality of life (HRQoL), fatigue, emotional well-being	PsA impact of disease (PsAID) [26]
Systemic inflammation	C-reactive protein
Participation	Work productivity and activity impairment (WPAI) [27], PSAID [26]
Health economic evaluation	EuroQol (EQ-5D-5L) and health resource utilisation
Health economic evaluation	EuroQol (EQ-5D-5L) and health resource utilisation
Common adverse events	Common adverse events reported by patient related to the biologic DMARD.

EuroQoL – European quality of life index, HAQ – health assessment questionnaire, PASI – psoriasis area and severity score, PsAID – PsA impact of disease, SJC – swollen joint count, SPARCC – Spondyloarthritis research consortium of Canada, TJC – tender joint count, VAS – visual analogue scale, WPAI – work productivity and activity impairment,

Statistical Analysis Plan

A detailed statistical analysis plan (SAP) will be drafted early in the trial and will be finalised and pre-registered prior to any primary outcome analysis. All analyses will be on an intention to treat basis,

that is according to group a patient is randomised to, irrespective of compliance with treatment allocation. A per-protocol population will be defined, and the primary outcome re-analysed on this population.

The primary outcome will be assessed via logistic regression adjusted for activated Th17 level as a continuous indicator, treatment and an interaction between the two; the stratification factors of study centre and psoriasis severity will also be included. 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. The primary focus is on the interaction between biomarker and treatment; the p-value for this interaction will be reported and considered significant if it falls below 0.05. Mean response rate by treatment and by the four groups defined by treatment and biomarker (high/ low) will be reported along with 95% CIs.

It is assumed that there is no difference between randomised group difference in MDA response at 24 weeks. To test this, response rates for the randomised groups will be reported. An odds ratio, and its 95% CI, will come from the same model as used in the primary analysis but without the treatment/ biomarker interaction (Th17 biomarker will be included as continuous variable).

The secondary outcome of MDA at the 12 (adalimumab)/ 16 (secukinumab) week time point will be analysed using the same model as defined for the primary outcome but with MDA at the secondary time point as the response. All other secondary outcomes analysed as part of this trial are continuous and will be analysed using the same model but adjusting for the appropriate variables in each analysis. All continuous outcomes at 24 weeks will be analysed using a mixed effects linear regression model. The model will include study centre as a random effect, baseline PASI (continuous), Th17 proportions (continuous), baseline measures of the outcome being analysed and randomised treatment as fixed effects. A treatment by biomarker interaction will be included in the model to formally test the interaction between treatment and biomarker.

The appropriateness of the assumption of approximate normality of the residuals for the analysis models will be assessed graphically.

Missing data will be minimised by careful data management. Missing data will be described with reasons given where available. Missing data analysis will be performed on the primary analysis only. 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 missing data can be treated as missing at random. If it is plausible that the data is missing not at random, a search for factors not included in the primary analysis model that explain missingness will be performed and if variables are

found, multiple-imputation will be utilised, using the primary analysis model but including these variables. If no variables are identified, multiple-imputation will not be performed.

Additional hypothesis generating analyses will be undertaken to investigate alternative potential models for predicting response to different classes of biologic. Analysis methods for exploratory, lab-based or machine learning outcomes will not be defined in this paper as these are not performed as part of the compilation of the final statistical report.

Monitoring

The study is managed by a trial management committee including the CI, laboratory lead and OCTRU staff. An independent trial steering committee and data safety and monitoring committee oversee the OPTIMISE study. They are independent of the study sponsor and full charters are available on request from OCTRU. OCTRU will audit the study once in its lifetime and also perform a detailed review prior to issuing green light in line with OCTRU SOPs. These audits are independent from the investigators but not independent from the Sponsor.

Patient and public involvement (PPI)

The lack of data informing the choice of biologics is frustrating for clinicians and for patients who want to know in advance which therapy would be best for them. This was reflected in the recent PsA James Lind Priority Setting Partnership where the question "What is the best strategy for managing patients with psoriatic arthritis including non-drug and drug treatments?" was ranked highest in the top ten unmet needs.[18] Patient research partners from the British PsA Consortium (BritPACT) assisted with the design of the study including research question, timing of follow up visits (to minimise burden for participants) and selection of outcome measures. Four patient partners living with PsA sit on the trial steering committee overseeing the trial throughout and helping with dissemination of the future results.

Ethics and dissemination

The OPTIMISE trial is being conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. Approval from the Health Research Authority and the North West – Preston Research Ethics Committee with reference 21/NW/00016. Collection of personal data is minimised within the study, with identifiable data being held securely in order to maintain confidentiality before, during and after the trial.

The deliverables from this project will include peer reviewed publications describing the clinical and mechanistic results of the study and a predictive panel that could predict response to IL-17 and/or TNF inhibitor therapy in PsA. This panel will be used to develop a more feasible and scalable companion

diagnostic for clinical practice. This could be tested in further large-scale studies in the next step towards routine implementation of precision medicine in PsA. Health economic data from our study will assist in the planning of future cost effectiveness trials. A biobank repository of remaining biological samples will allow future mechanistic and precision medicine biomarker work with additional funding. Data may be shared with other research groups on reasonable request following the completion of the primary analysis.

Discussion

Early optimisation of biologic therapy will have numerous benefits including increasing the likelihood of a significant response and good outcome and reducing delay and risks of potentially ineffective therapies. Although further confirmatory studies outlined above would be required, there is great potential for this work to impact on UK NICE guidance for the use of biologics in PsA in the UK, particularly if this approach demonstrates health economic benefits. This would provide clear efficiency savings to both patients and the NHS as 3-6 month courses of ineffective therapies would be avoided.

Role of study sponsor and funder

The study is sponsored by the Research Governance, Ethics and Assurance Team, University of Oxford (rgea.sponsor@admin.ox.ac.uk). The study is manged by the Oxford Clinical Trials Research Unit (OCTRU), at the University of Oxford.

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Competing interests statement

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HA is a full time employee of Astrazeneca and former employee of UCB. He own shares in UCB, AZ and GSK. He have previously received unrestricted research funding from UCB. He have received consulting and speaker fees from UCB, Novartis, Pfizer and Abbvie.

PB has received research support from Regeneron, Novartis and GSK.

CG has received grants/contracts from AstraZeneca, BMS, Eli Lilly, Galvani, GSK, Istesso, Janssen, MedAnnex, MiroBio, Revolo, UCB; Consulting fees from AstraZeneca, BMS, Galvani, MedAnnex, Medincell; Payment/honoraria from Abbvie, BMS, UCB.

BK has received research support from Eli Lilly and Novartis and consultation fees/speaker fees from Abbvie, Eli Lilly, Galapagos, Janssen, Novartis, Pfizer and UCB.

IBM has received research support, consultation fees and honoraria from Abbvie, Amgen, BMS, Causeway Therapeutics, Cabaletta, Eli Lilly, Gilead, Janssen, Novartis, Pfizer, Sanofi, UCB, Evelo, Compugen, AstraZeneca, Moonlake. He has stock or stock options in Evolo, Cabaletta, Compugen, Causewauy Therapeutics and Dextera. He is a board members/trustee of NHS GGC, Evolo and Versus Arthritis.

DR Consultant to OMASS therapeutics Ltd. Scientific advisory board of Avicenna Biosciences Inc.

SS has received institutional grants/research support from AbbVie, Amgen, Eli Lilly, GSK, Janssen and UCB; and has received speaker/consultancy fees from AbbVie, Astra Zeneca, Eli Lilly, Janssen and UCB.

LST has previously received research support from Sanofi, UCB, GSK and Novartis, outside of the work described here.

LCC has received grants/research support from AbbVie, Amgen, Celgene, Eli Lilly, Janssen, Novartis, Pfizer and UCB; worked as a paid consultant for AbbVie, Amgen, Bristol Myers Squibb, Celgene, Eli Lilly, Gilead, Galapagos, Janssen, Moonlake, Novartis, Pfizer and UCB; and has been paid as a speaker for AbbVie, Amgen, Biogen, Celgene, Eli Lilly, Galapagos, Gilead, GSK, Janssen, Medac, Novartis, Pfizer and UCB.

The remainder of authors declare no conflicts of interest.

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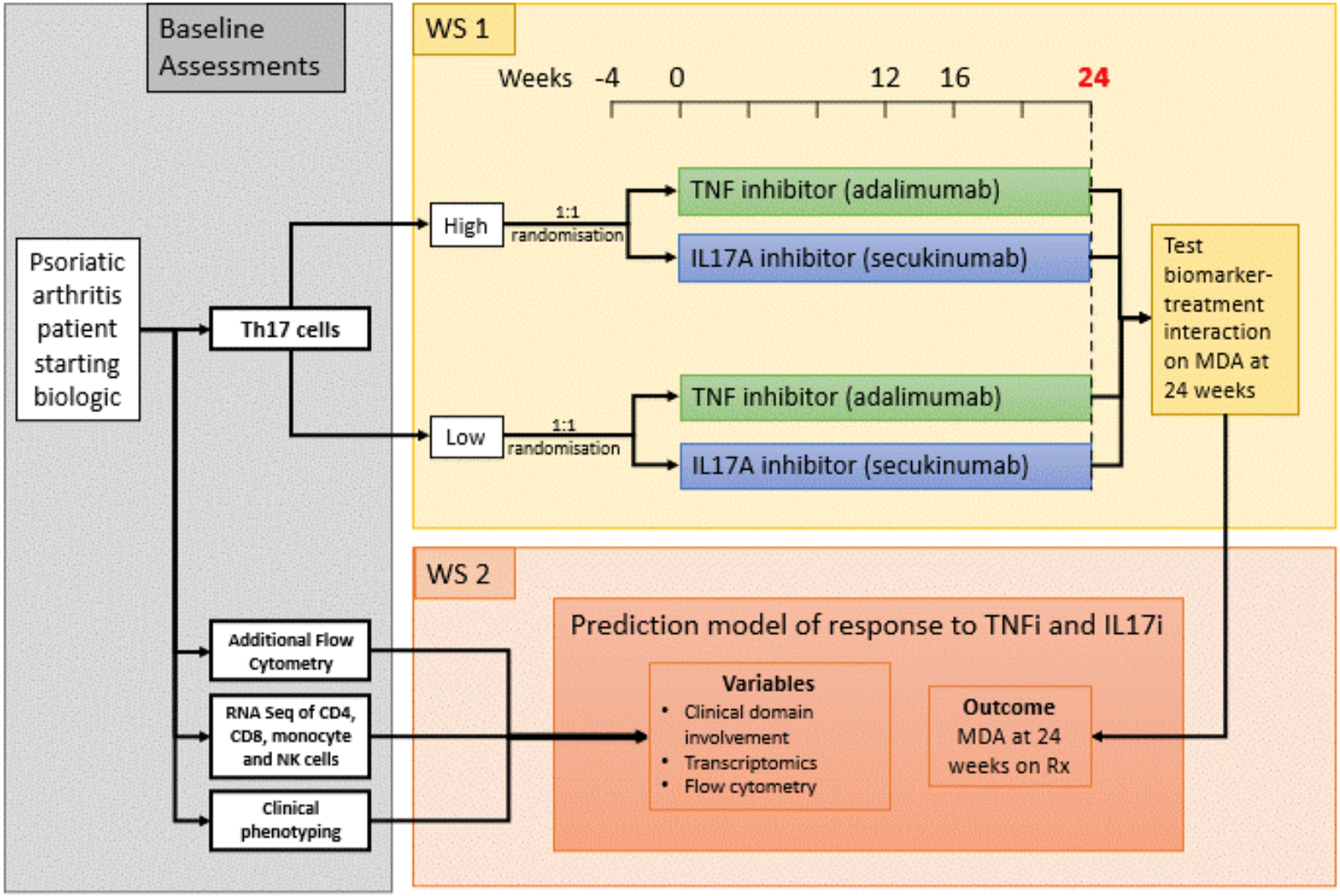
Figure 1 – study design



IL17A = interleukin 17A, MDA = minimal disease activity, NK = natural killer cells, TNF = tumour necrosis factor,

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	10
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	17

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	10
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	13
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14-15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3&17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Consent form attached
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	13
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	17
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Consent form attached
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	17

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Optimising Psoriatic Arthritis Therapy with Immunological Methods to Increase Standard Evaluation: The protocol of an open-label multi-centre, parallel-group, two arm randomised controlled study evaluation precision medicine approach in the treatment of psoriatic arthritis.

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Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Research methods
Keywords:	Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, RHEUMATOLOGY, Clinical Decision-Making, Clinical Trial

Title

Optimising Psoriatic Arthritis Therapy with Immunological Methods to Increase Standard Evaluation: The protocol of an open-label multi-centre, parallel-group, two arm randomised controlled study evaluation precision medicine approach in the treatment of psoriatic arthritis.

Short title

The OPTIMISE Study

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Abstract – 299/300 words

Introduction – Psoriatic arthritis (PsA) affects around 150,000 people in the UK of whom around 50% require treatment with biologics. The most used biologics for PsA target tumour necrosis factor (TNF) or interleukin-17A (IL-17A). About 50% of patients respond to each but it is not currently possible to predict response for individual patients, necessitating sequential treatment steps. A recent proof of concept study in PsA suggested that using peripheral immunophenotype to choose therapy could improve time to treatment response.

This study will test the hypothesis, within an open-label parallel-group biomarker-stratified multi-centre randomised controlled trial, that the baseline proportion of CD4+ T cells with an activated Type 17 immunophenotype (Th17 levels) predicts response to IL-17A or TNF inhibitors in PsA. Additional analyses will identify if the model can be refined by combining additional clinical and immunophenotypic factors. Statistical modelling will be used to predict the likely effectiveness of these approaches compared with standard care.

Methods and analysis: Patients with PsA eligible to start their first biologic as part of standard care are recruited and baseline blood tests taken for immunophenotyping. Participants are stratified equally by Th17 levels and randomised 1:1 to receive either TNF (adalimumab) or IL-17A (secukinumab) inhibitors. The primary analysis will establish the interaction between baseline immunophenotype and treatment on the primary outcome (achievement of minimal disease activity criteria at week 24). In secondary analysis, modelling will identify if this prediction model can be optimised further by incorporating clinical phenotypes and additional immunophenotyping techniques.

Ethics and dissemination – Ethical approval for the study was granted by the North West Preston Research Ethics Committee (ref 21/NW/0016). Dissemination will be via conference presentations and peer reviewed publications, aiming to impact on treatment guidelines.

Registration - ISRCTN17228602

Strengths and limitations (5 bullet points related to methods)

- The OPTIMISE study is the first powered randomised controlled trial investigating a precision medicine approach to biologic selection in PsA.
- Broad eligibility criteria, in keeping with current UK treatment recommendations, increase the generalisability of the trial results to clinical practice.

- Both participants and clinicians are blinded to the immunophenotyping data minimising bias in the analysis.
- Detailed immunophenotyping using multiple laboratory approaches will maximise the chances of identifying key predictive markers for response.
- Of note, immunophenotyping requires considerable cell processing and is not yet optimised for routine diagnostic use.

Word count 3087/4000 words

Introduction

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 levels reported for 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 an empiric 'step up' 'trial-and-error' approach using different conventional disease-modifying anti-rheumatic drugs (DMARDs) followed by biologic DMARDs if patients do not respond [1, 6]. Approximately 50% of patients with PsA will require biologic therapy [7] with four key mode of action drugs available. The most commonly used biologic treatments for PsA target one of two main immunological pathways: tumour necrosis factor (TNF), or interleukin (IL) 17. Arthritis response rates to both drugs are similar, with 60-70% of patients achieving at least a partial response. In clinical practice, biologic therapies need to be used for a minimum of 12-16 weeks before response can be evaluated [1, 6], with assessment of achievement of treatment target later [8]. For many patients this means protracted administration of a therapy that may never work, in addition to financial and clinical NHS costs.

Two head-to-head parallel-group randomised studies comparing TNF and IL-17A inhibitors in PsA have been performed showing no significant differences in peripheral arthritis outcomes.[9, 10] Currently, clinicians select therapies based on a limited clinical phenotype, such as differentiation in skin psoriasis, comorbidities, personal experience and cost. Despite similar responses at a group level, we know that some people who fail to respond to a first biologic will have a good response when they switch to a drug with a different mechanism of action [11] suggesting that disease immunopathogenesis varies between individuals. However, treatment in these studies was randomly allocated, with only one previous study in PsA with any precision medicine element.

This study in Japan evaluated the use of baseline CD4+ T cell immunophenotype characteristics to inform selection of biologic therapy [12]. They defined four groups based on predetermined cut-offs for high and low levels of Th1 and Th17 cells, based on quartiles in healthy controls. Sixty-four PsA patients starting biologic therapy were randomly divided into a standard care group (IL-12/23, IL-17A or TNF inhibitors) and a precision medicine group (n=26) in which the choice of therapy was based on the peripheral blood lymphocyte analysis. The precision medicine group had significantly higher rates of ACR20 response and low disease activity, although other measures, including psoriasis responses, were not significantly different. The study was not powered to compare the treatment groups and

did not include a pre-specified primary outcome. However, the results are promising, and the study urgently requires confirmation.

A more rational approach to treatment selection has the potential to make a substantial contribution to patient care by increasing the chance of identifying the biologically rational treatment for the patient. Thus, the primary aim of the OPTIMISE (Optimising Psoriatic arthritis Therapy with Immunological Methods to Increase Standard Evaluation) study is to identify a peripheral immunophenotype that can predict response to biological therapy in PsA and facilitate a stratified approach to treatment.

Objectives

Our primary objective is to establish the interaction between baseline immunophenotype (proportion of CD4+ T cells with an activated Th17 cell profile) and treatment (IL-17A or TNF inhibitor therapy) on the proportion of PsA patients achieving the minimal disease activity (MDA) criteria at week 24 (primary outcome).

Our secondary objectives will compare responses to both medications dependent on intracellular IL-17 levels and immune-subset transcriptomic signatures to see if additional immunological markers can predict response to either drug. Treatment response from a patient's perspective is assessed through patient reported outcome measures. We will also explore changes in the immunological markers with treatment and assess if these correlate with clinical response. These objectives are all summarised in Table 1.

Table 1 – primary, secondary and exploratory objectives for the OPTIMISE trial

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective To test whether the clinical response to TNF and IL-17A inhibitor therapy in participants with PsA differs according to the level of baseline activated Th17 cells.	Clinical response as measured by the minimal disease activity (MDA) criteria	Immunophenotype data at baseline and clinical response at week 24.
Secondary Objectives To test whether the clinical response to TNF and IL-17A inhibitor therapy in participants with PsA differs according to intracellular IL-17 levels.	Clinical response as measured by the minimal disease activity (MDA) criteria	Immunophenotype data at baseline and clinical response at week 12/16 and week 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 week 24.
To explore if the immune subset-specific transcriptomic signature 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 scores and in overall disease as measured by the PsA disease activity score (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	Immunophenotype data at baseline and clinical

	outcomes including PsAID, SF36 and WPAI	response at week 12/16 and 24.
To use the immune subset-specific transcriptomic signature to identify a limited number to of transcriptomic biomarkers that can be validated in whole blood.	Cell specific transcriptomic data and whole blood transcriptomes	Immunophenotype data at baseline and week 24.
To use the immune subset-specific transcriptomic signature to define the pathways driving biologic-refractory disease.	Cell specific transcriptomic data and whole blood transcriptomes	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 with additional immunophenotypic (intracellular CD4 Th17 frequency, CD8 Tc17 frequency, MAIT cell frequency, immune transcriptomic signature) factors to develop a predictive model for response to IL-17A and/or TNF inhibitor therapy in PsA.	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.
To test whether the clinical response to TNF and IL-17A inhibitor therapy in participants with PsA differs according to the level of baseline activated Th17 cells.	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 transcriptomics 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.

Our exploratory objective is to use machine learning and predictive modelling to combine baseline clinical phenotypic markers such as disease duration and clinical expression of disease, with additional immunophenotypic (intracellular cytokine staining to determine IL-17A+CD4+ (Th17) or IL-17A+CD8+ (Tc17) frequencies, MAIT cell frequency, immune transcriptomic signature) factors to develop an optimal predictive model for individual responses to IL-17A and/or TNF inhibitor therapy in PsA.

Our exploratory mechanistic objectives are:

- To understand if the activated Th17 surface and intracellular signature (and possibly also other IL-17 signatures) resolve after treatment with IL-17A inhibitors and how these are altered after TNF inhibitor therapy with additional focus on the polyfunctional cells producing multiple cytokines.

- To understand if changes in the activated Th17 surface and intracellular signature (and possibly other IL-17 signatures) differ in treatment responders and non-responders.
- To explore if immune subset-specific transcriptomic signatures can be used to predict efficacy of IL-17A and TNF inhibitor therapies either alone or in combination with the activated surface and intracellular Th17 signatures.
- To use the identified transcriptomic signature to identify a limited number of transcriptomic biomarkers that can be validated in whole blood.
- To use the immune subset-specific transcriptomic signature to define the pathways driving biologic-refractory disease.
- To establish a biobank of samples at the end of this analysis to allow future investigation of novel scientific techniques and biomarkers within this population (with future separate funding).

Methods and analysis

Study design

The OPTIMISE study is an open-label parallel-group biomarker-stratified multi-centre randomised controlled trial of adults with PsA where participants are randomised to either TNF or IL-17A inhibitors, testing whether this or other immunological markers can predict achievement of the MDA criteria after 24 weeks on therapy (figure 1). This paper describes v7.0 (dated 24May2023) of the protocol. Changes in the protocol since v1.0 include

- Initial modification in response to research ethics committee review
- Addition of exclusion criteria for those unwilling to follow contraceptive advice
- Inclusion of eligibility for those who have failed 1 conventional DMARD but are eligible for treatment under local guidelines
- Changes to study recruitment dates and inclusion of patient identification centres (PICs)
- Changes to sample size (as outlined below)

Selection of Population

The population included are adults (≥18 years old) with PsA fulfilling the CASPAR criteria who are due to start biological therapy for their PsA according to established UK eligibility criteria. This typically requires patients to have failed to respond to ≥2 conventional DMARDs and to have active disease demonstrated by ≥3 tender/swollen joints. Patients with previous exposure to biological therapies or

those who have contraindications to either drug are excluded from participation. Full inclusion and exclusion criteria are shown in Table 2.

Table 2 – Inclusion and exclusion criteria for the OPTIMISE trial

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 • Is eligible and planned to have biologic therapy for psoriatic arthritis using local guidelines or using NICE/SMC criteria (failure of ≥1 conventional DMARDs and ≥3 tender AND ≥3 swollen joints).
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
• 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.

Randomisation, blinding and allocation concealment

Prior to randomisation, we record the therapy that was planned by the physician if they had not been recruited to the trial.

Eligible and consented patients are randomised centrally by clinical trial unit staff using the bespoke computerised trial unit specific randomisation system. Patients are randomised in a 1:1 allocation ratio to either TNF (adalimumab) or IL-17A (secukinumab) inhibitor. The randomisation uses a minimisation algorithm to ensure balanced allocation across the treatment groups, stratified by activated Th17 proportion (≤/>1.58%), psoriasis severity (psoriasis area and severity index [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 to ensure the unpredictability of treatment allocation. There is no blinding of therapy allocation for patients or clinicians so no allocation code or code-breaking procedure is required, however the baseline immunophenotype data will be blinded from all participants and clinical study site personnel, while laboratory staff will be blinded to the allocated therapy. Unblinding should not be required during the study as it will not have clinical relevance to treatment decisions.

Interventions, patient follow-up, visits and trial procedures

Following consent, patients undergo a baseline clinical assessment and blood is taken for immunophenotyping. Fresh peripheral blood samples (50mls) are couriered to one of the three laboratory hub sites (Oxford, Glasgow, London) for processing within 6 hours and are then cryopreserved for mechanistic cellular work (peripheral blood mononuclear cells [PBMCs]) or whole blood RNA sequencing). Our preliminary analysis shows that peripheral Th17 surface and intracellular signatures at 6 hours are comparable to freshly isolated samples. The measurement of the biomarker will be processed simultaneously with local processing of standard clinical safety screening for biological therapies (e.g. hepatitis/TB screening), avoiding delay to patients' treatment.

Analysis will be performed on cryopreserved samples rather than fresh samples to allow standardisation across centres, avoid delays to samples arriving late in the day and avoid issues with temporary unavailability of essential laboratory machinery such as flow cytometers. In the primary laboratory analysis, the samples will undergo ten colour flow cytometry. In the first instance, activated Th17 frequencies will be identified based on CCR6+ and CXCR3- expression on CD3+CD4+CD8- T cells and co-expression of known T cell activation markers CD38 and HLA-DR, as described in the Miyagawa study[12]. The proportion of activated Th17 cells will be included in the randomisation process to ensure equal stratification across the treatment arms.

The TNF inhibitor used in the study is adalimumab (any brand, including biosimilars) and is given at the usual licensed dose of 40 mg by subcutaneous injection every 2 weeks, with no loading doses. The IL-17A inhibitor used is secukinumab, brand name Cosentyx, and is given at the usual licensed dose which varies based on the level of baseline skin psoriasis. The usual recommended dose as a first line biologic in PsA is 150mg by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4 followed by a monthly maintenance dose. For patients with concomitant moderate to severe plaque psoriasis, the recommended dose is 300mg by subcutaneous injection at the same timepoints. This study therefore follows 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 from 150mg to 300mg in the case of a partial response to treatment as per the licence is permitted. Both drugs are provided from usual NHS stock and are self-administered by the patients following standard initial training, as per usual clinical practice.

The study involvement for each participant is 24 weeks plus the screening period (typically 4-8 weeks). Drug treatment is started at baseline and continued for the 24 weeks with study 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. Patients recruited at the hub sites are also asked to attend at week 4 for a research blood sample to be taken. After the 24-week study treatment period, participants who have responded well to treatment can continue on treatment following the end of the study period or switch to another treatment in line with usual NHS practice. Any patient discontinuing treatment for clinical reasons will be encouraged to attend for study visits and any treatment changes will be documented.

Sample size

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 [13-15], 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%.

Initially, the analysis planned to detect a biomarker-treatment relative interaction effect of 0.2, with >90% power and 5% type I error, using a difference in the MDA-response rate according to whether the proportion of activated Th17 cells 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 TNF inhibitors, and 40% and 60% for participants with low/high Th17 treated with IL-17A inhibitors This resulted in an original sample size of 424 participants.

However, this analysis would have converted the Th17 levels recorded in the trial into a dichotomous variable split around the median, creating two subgroups: 'high Th17' and 'low Th17'. Applying such a dichotomy causes information loss and reduces available power. Therefore, during recruitment an amendment was proposed and approved to use the proportion of activated Th17 cells in the analysis as a continuous outcome, whilst assuming the same relative interaction effect of 0.2, type I error rate of 0.05 and 90% power. This resulted in a reduction in the required sample size to 240 participants without a loss of power. This assumes a 'main effect' of treatment response (the difference in response between treatment arms distinct from the interaction effect) of 0.2, and no direct correlation between Th17 level and response after including the interaction effect.

Recruitment

Enrolment occurs within rheumatology outpatient clinics at participating UK hospital sites. Potential participants are approached by their clinical team after the decision has been made to start biologic therapy as part of standard clinical care and guidance. Written consent is obtained from potential trial participants by the principal investigator or a designated member of study staff using the approved consent form (see supplementary file). With 17 sites, it is estimated that recruitment will complete in 36 months. The trial opened for recruitment in January 2022 and the estimated completion date is December 2024.

Outcomes

The primary outcome will be treatment response as measured by the proportion of patients achieving the MDA criteria [16] at 24 weeks (see Table 3).

Table 3 – Minimal disease activity (MDA) criteria

Patients are classified as being in MDA when they achieve any 5 or more of the following 7 criteria
Tender joint count ≤ 1
Swollen joint count ≤ 1
Psoriasis area and severity index ≤ 1
Enthesitis score ≤ 1
Patient global visual analogue scale of disease activity ≤ 20mm
Patient visual analogue scale of pain ≤ 15mm
Health assessment questionnaire score ≤ 0.5

Individual secondary outcome measures covering all of the new 2016 Outcome Measures in Rheumatology Clinical Trials (OMERACT) core and strongly recommended domains for PsA studies [17] are collected at all timepoints, with the exception of radiographic damage which is inappropriate in a short duration, active comparator study. The secondary outcome measures are listed in Table 4. The electronic case report form (eCRF) system REDCap is being used to collect the data.

Table 4 – secondary outcome measures for the OPTIMISE trial

Musculoskeletal disease activity	Physician global visual analogue scale (VAS), 68 tender joint count (TJC) and 66 swollen joint count (SJC) [18], Leeds [19] and Spondyloarthritis Research Consortium of Canada (SPARCC) [20] enthesitis indexes, dactylitis count [21],
Psoriasis disease activity	PASI [22] and nail disease VAS
Pain	Patient pain VAS [18]
Global	Global disease activity VAS [23]
Physical function	HAQ [24]
Health related quality of life (HRQoL), fatigue, emotional well-being	PsA impact of disease (PsAID) [25]
Systemic inflammation	C-reactive protein
Participation	Work productivity and activity impairment (WPAI) [26], PSAID [25]
Health economic evaluation	EuroQol (EQ-5D-5L) and health resource utilisation
Health economic evaluation	EuroQol (EQ-5D-5L) and health resource utilisation
Common adverse events	Common adverse events reported by patient related to the biologic DMARD.

EuroQoL – European quality of life index, HAQ – health assessment questionnaire, PASI – psoriasis area and severity score, PsAID – PsA impact of disease, SJC – swollen joint count, SPARCC – Spondyloarthritis research consortium of Canada, TJC – tender joint count, VAS – visual analogue scale, WPAI – work productivity and activity impairment,

Statistical Analysis Plan

A detailed statistical analysis plan (SAP) will be drafted early in the trial and will be finalised and pre-registered prior to any primary outcome analysis. All analyses will be on an intention to treat basis, that is according to group a patient is randomised to, irrespective of compliance with treatment allocation. A per-protocol population will be defined, and the primary outcome re-analysed on this population.

The primary outcome will be assessed via logistic regression adjusted for activated Th17 level as a continuous indicator, treatment and an interaction between the two; the stratification factors of study centre and psoriasis severity will also be included. 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. The primary focus is on the interaction between biomarker and treatment; the p-value for this interaction will be reported and considered significant if it falls below 0.05. Mean response rate by treatment and by the four groups defined by treatment and biomarker (high/ low) will be reported along with 95% CIs.

It is assumed that there is no difference between randomised group difference in MDA response at 24 weeks. To test this, response rates for the randomised groups will be reported. An odds ratio, and its 95% CI, will come from the same model as used in the primary analysis but without the treatment/ biomarker interaction (Th17 biomarker will be included as continuous variable).

The secondary outcome of MDA at the 12 (adalimumab)/ 16 (secukinumab) week time point will be analysed using the same model as defined for the primary outcome but with MDA at the secondary time point as the response. All other secondary outcomes analysed as part of this trial are continuous and will be analysed using the same model but adjusting for the appropriate variables in each analysis. All continuous outcomes at 24 weeks will be analysed using a mixed effects linear regression model. The model will include study centre as a random effect, baseline PASI (continuous), Th17 proportions (continuous), baseline measures of the outcome being analysed and randomised treatment as fixed effects. A treatment by biomarker interaction will be included in the model to formally test the interaction between treatment and biomarker.

The appropriateness of the assumption of approximate normality of the residuals for the analysis models will be assessed graphically.

Missing data will be minimised by careful data management. Missing data will be described with reasons given where available. Missing data analysis will be performed on the primary analysis only.

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 missing data can be treated as missing at random. If it is plausible that the data is missing not at random, a search for factors not included in the primary analysis model that explain missingness will be performed and if variables are found, multiple-imputation will be utilised, using the primary analysis model but including these variables. If no variables are identified, multiple-imputation will not be performed.

Additional hypothesis generating analyses will be undertaken to investigate alternative potential models for predicting response to different classes of biologic. Analysis methods for exploratory, lab-based or machine learning outcomes will not be defined in this paper as these are not performed as part of the compilation of the final statistical report.

Monitoring

The study is managed by a trial management committee including the CI, laboratory lead and OCTRU staff. An independent trial steering committee and data safety and monitoring committee oversee the OPTIMISE study. They are independent of the study sponsor and full charters are available on request from OCTRU. OCTRU will audit the study once in its lifetime and also perform a detailed review prior to issuing green light in line with OCTRU SOPs. These audits are independent from the investigators but not independent from the Sponsor.

Patient and public involvement (PPI)

The lack of data informing the choice of biologics is frustrating for clinicians and for patients who want to know in advance which therapy would be best for them. This was reflected in the recent PsA James Lind Priority Setting Partnership where the question "What is the best strategy for managing patients with psoriatic arthritis including non-drug and drug treatments?" was ranked highest in the top ten unmet needs.[27] Patient research partners from the British PsA Consortium (BritPACT) assisted with the design of the study including research question, timing of follow up visits (to minimise burden for participants) and selection of outcome measures. Four patient partners living with PsA sit on the trial steering committee overseeing the trial throughout and helping with dissemination of the future results.

Ethics and dissemination

The OPTIMISE trial is being conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. Approval from the Health Research Authority and the North West – Preston Research Ethics Committee with reference 21/NW/00016. Collection of personal data is minimised

within the study, with identifiable data being held securely in order to maintain confidentiality before, during and after the trial.

The deliverables from this project will include peer reviewed publications describing the clinical and mechanistic results of the study and a predictive panel that could predict response to IL-17 and/or TNF inhibitor therapy in PsA. This panel will be used to develop a more feasible and scalable companion diagnostic for clinical practice. This could be tested in further large-scale studies in the next step towards routine implementation of precision medicine in PsA. Health economic data from our study will assist in the planning of future cost effectiveness trials. A biobank repository of remaining biological samples will allow future mechanistic and precision medicine biomarker work with additional funding. Data may be shared with other research groups on reasonable request following the completion of the primary analysis.

Discussion

The OPTIMISE study is the first powered randomised, controlled trial investigating a precision medicine approach to biologic selection in PsA. Although treatment is open label, blinding to the immunophenotyping data will minimise any bias in the study. This work has the potential to increase the likelihood of a significant response and good outcome and reducing delay and risks of potentially ineffective therapies. The study has been designed with broad eligibility criteria to increase generalisability to clinical practice and reflect patients currently treated with these drugs in the UK. Detailed immunophenotyping will maximise the chance of identifying key predictive markers of response. Although immunophenotyping requires considerable cell processing and this would not be feasible in the same fashion within clinical laboratories, we believe that these markers can be further developed into practical tests that could be used in hospitals for routine clinical use. Further confirmatory studies outlined above would be required, there is great potential for this work to impact on UK NICE guidance for the use of biologics in PsA in the UK, particularly if this approach demonstrates health economic benefits. This would provide clear efficiency savings to both patients and the NHS as 3-6 month courses of ineffective therapies would be avoided.

Authors contributions

HA, PB, CG, BK, IBM, DR, SS, LST and LCC are responsible for the conception of the study. AO, HA, LB, MB, PB, AF, CG, BK, SL, IBM, DR, SS, LST, ATV, NY and LCC designed the protocol. AO and LCC wrote the original draft. All authors revised the draft.

Role of study sponsor and funder

The study is sponsored by the Research Governance, Ethics and Assurance Team, University of Oxford (rgea.sponsor@admin.ox.ac.uk). The study is manged by the Oxford Clinical Trials Research Unit (OCTRU), at the University of Oxford.

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Data availability statement – Data are available upon reasonable request. Participant-level dataset and statistical code will be made available upon reasonable request to the Oxford Clinical Trials Research Unit and the CI, once the study findings have been published in full. Some specific data items may not be shared in order to maintain participant anonymity.

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Competing interests statement

The institutions of all co-authors received funding from the NIHR-MRC-EME programme (NIHR129023) for conducting this research.

HA is a full time employee of Astrazeneca and former employee of UCB. He own shares in UCB, AZ and GSK. He have previously received unrestricted research funding from UCB. He have received consulting and speaker fees from UCB, Novartis, Pfizer and Abbvie.

PB has received research support from Regeneron, Novartis and GSK.

CG has received grants/contracts from AstraZeneca, BMS, Eli Lilly, Galvani, GSK, Istesso, Janssen, MedAnnex, MiroBio, Revolo, UCB; Consulting fees from AstraZeneca, BMS, Galvani, MedAnnex, Medincell; Payment/honoraria from Abbvie, BMS, UCB.

BK has received research support from Eli Lilly and Novartis and consultation fees/speaker fees from Abbvie, Eli Lilly, Galapagos, Janssen, Novartis, Pfizer and UCB.

IBM has received research support, consultation fees and honoraria from Abbvie, Amgen, BMS, Causeway Therapeutics, Cabaletta, Eli Lilly, Gilead, Janssen, Novartis, Pfizer, Sanofi, UCB, Evelo, Compugen, AstraZeneca, Moonlake. He has stock or stock options in Evolo, Cabaletta, Compugen, Causewauy Therapeutics and Dextera. He is a board members/trustee of NHS GGC, Evolo and Versus Arthritis.

DR Consultant to OMASS therapeutics Ltd. Scientific advisory board of Avicenna Biosciences Inc.

SS has received institutional grants/research support from AbbVie, Amgen, Eli Lilly, GSK, Janssen and UCB; and has received speaker/consultancy fees from AbbVie, Astra Zeneca, Eli Lilly, Janssen and UCB.

LST has previously received research support from Sanofi, UCB, GSK and Novartis, outside of the work described here.

LCC has received grants/research support from AbbVie, Amgen, Celgene, Eli Lilly, Janssen, Novartis, Pfizer and UCB; worked as a paid consultant for AbbVie, Amgen, Bristol Myers Squibb, Celgene, Eli Lilly, Gilead, Galapagos, Janssen, Moonlake, Novartis, Pfizer and UCB; and has been paid as a speaker for AbbVie, Amgen, Biogen, Celgene, Eli Lilly, Galapagos, Gilead, GSK, Janssen, Medac, Novartis, Pfizer and UCB.

The remainder of authors declare no conflicts of interest.

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Figure legend

Figure 1 – OPTIMISE study design

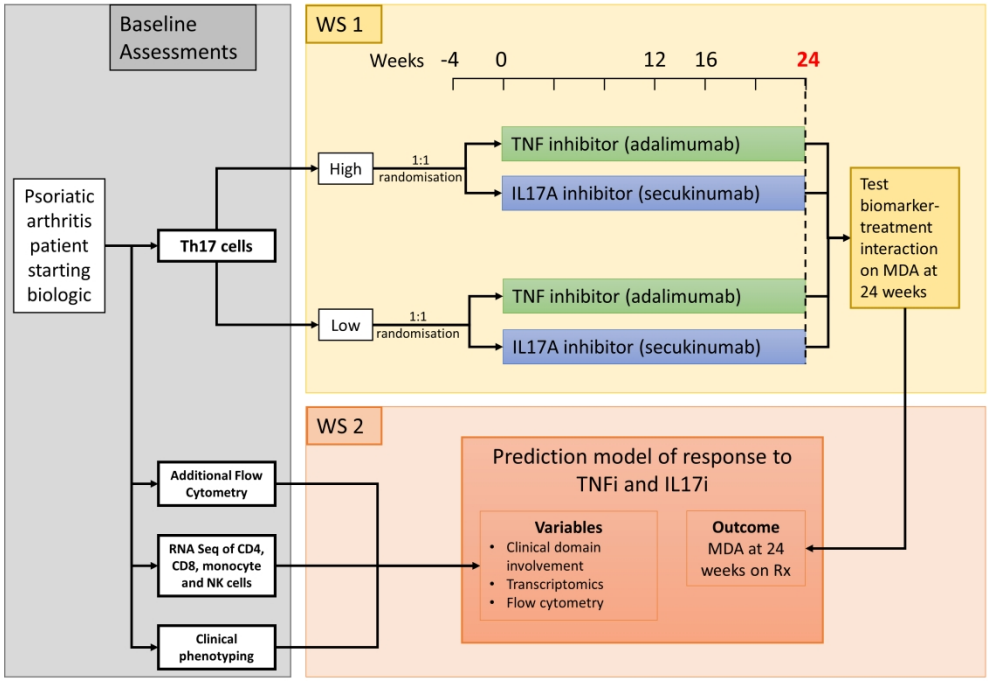

Figure 1 – OPTIMISE study design

275x190mm (300 x 300 DPI)

IRAS ref: 17/SC/0556

Multicentre Observational Intervention assessing Treat to Target Outcomes in Psoriatic Arthritis (MONITOR-PsA)

Principal Investigator details: Dr Laura Coates

MAIN: CONSENT FORM -

Title of Project: A multicentre observational psoriatic arthritis cohort study addressing real-life outcomes of a treat to target approach in routine clinical practice.

Participant Initials				**Participant No.**		**Site Code**	

Please write your initials in the each of the boxes below if you agree

1	I confirm that I have read and understand the information sheet V……. dated ……/……./……for the above study, that I have had the opportunity to ask questions and that I have received satisfactory answers to the questions that I have asked.	☐
2	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
3	I understand that sections of any of my medical notes may be looked at by responsible individuals from the Sponsor, regulatory authorities and Host NHS organisations where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	☐
4	I understand that a copy of my details will be sent to the study coordinating team in Oxford using secure encrypted electronic transfer. These details may be used to check contact details using NHS Digital and other central UK NHS bodies, and to provide other basic study-related information that may be needed for follow up. This will allow the study team to contact you if you miss a clinic visit.	☐

UNIVERSITY OF OXFORD

Oxford University Hospitals NHS
NHS Foundation Trust

MONITOR

OPTIONAL:

Use of data:

You can agree to clauses 1 and/or 2, below:

		Please initial one box under Yes or No	
		YES	**NO**
1	I agree for my personal information to be stored confidentially and securely by the study team, with linked pseudonomysed clinical and genetic data (including from any samples I give), so that they can contact me in the future to invite me to participate in any research studies related to my condition.	☐	☐
2. a)	I understand that the study team may make a random selection of some participants and invite those individuals to participate in the treatment arm of other research studies of treatment (including clinical trials of medicines).	☐	☐

Giving of samples:

If you do agree to give samples, we would ask that you agree to all of the clauses in this section.

3	I agree to donate blood, urine and faecal samples at each assessment.	☐	☐
4 a)	I understand that these samples will be used in genetic and biomarker research, aimed at understanding the genetic influences of diseases. However, the results of these investigations are unlikely to have any implications to me personally.	☐	☐
4 b)	I agree that any blood samples I donate for the study will be considered a gift to the University of Oxford and I understand I will not gain any direct personal or financial benefit from them.	☐	☐

Future use of samples:

If you do agree to give samples, the below clauses are regarding their future use. If you are happy for them to be used in future research, we would ask that you agree to all of the clauses in this section.

5 a)	I agree for my anonymised samples to be used in future research, here or abroad, which has ethics approval. I understand this research may involve commercial organisations, although I will gain no personal or financial benefit from this.	☐	☐
5 b)	I further understand that samples of DNA and RNA may be extracted for research aimed at understanding the genetic influences on disease and that the results of these investigations are unlikely to have any implications for me personally.	☐	☐

Oxford University Hospitals NHS
NHS Foundation Trust

MONITOR

_____	_____	_____
Name of Patient	Date	Signature

(Please print your name and date your own signature)

_____	_____	_____
Name of Person taking consent	Date	Signature

(Investigator/delegated medically – qualified sub investigator)

Original copy – site file

1 copy for patient; 1 copy to be kept with hospital notes; 1 copy for TMF at Co-ordinating centre.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	10
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	17

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	10
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	13
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14-15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3&17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Consent form attached
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	13
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	17
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	17
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Consent form attached
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	17

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.