Optimising Psoriatic Arthritis Therapy with Immunological Methods to Increase Standard Evaluation

Statistical Analysis Plan

Version 1.0 – 21Apr2026

Linked to SAP - Data definitions and Tables
Version 2.0 – 21Apr2026

Based on Protocol

Version 11.0 – 26Mar2026

Trial registration: IRAS 287528

Oxford Clinical Trials Research Unit (OCTRU)
Centre for Statistics in Medicine (CSM)

CONTENTS

1. INTRODUCTION

This document details the proposed data presentation and analysis for the main paper(s) and final study reports from the National Institute of Health Research Efficacy and Mechanism (Evaluation Grant NIHR 129023) funded Multicentre Randomised Controlled Trial for Optimising Psoriatic Arthritis Therapy with Immunological Methods to Increase Standard Evaluation (OPTIMISE). The results reported in these papers should follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy unless explicitly stated to be covered, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis (for example, to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (for example, data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial. This document follows published guidelines regarding the content of statistical analysis plans for clinical trial (Gamble et al).

The analysis strategy will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy. If reported, the analyses will be marked as post-hoc; the source of the suggestion will be acknowledged, and the reader will be advised to rely primarily on the pre-specified analysis for the interpretation of the results.

Any deviations from the statistical analysis plan will be described and justified in the final report of the trial. The analysis should be carried out by an identified, appropriately qualified and experienced statistician, who should ensure the integrity of the data during their processing. Examples of such procedures include quality control and evaluation procedures.

Integral to this Statistical Analysis Plan (SAP) is the SAP – Data Definitions and Tables document which will include full detailed descriptions of all key outcomes, including their definition, generation and how they will be reported at the end of the study.

1.1 Key personnel

Author(s) (Trial statistician)

Alex Zimmermann	Trial Statistician

Reviewers

Sofia Massa	Senior Statistician
Laura Coates	Chief Investigator

Approver

Sofia Massa	Senior Statistician
Laura Coates	Chief Investigator

1.2 Changes from previous version of SAP

A summary of key changes from earlier versions of SAP, with particular relevance to protocol changes that have an impact on the design, definition, sample size, data quality/collection and analysis of the outcomes is provided below.

Version number Issue date	Author of this issue	Protocol Version & Issue date	Significant changes from previous version together with reasons
V1.0_21Apr2026	Alex Zimmermann	Protocol_V11.0_26Mar2026	Not applicable as this is the 1st issue

2. BACKGROUND AND OBJECTIVES

Psoriatic arthritis (PsA) is an inflammatory arthritis occurring in approximately 15% of people with psoriasis, affecting around 150,000 people in the UK. The current first line biologics (drugs for patients who do not respond to standard arthritis drugs) for PsA are: tumour necrosis factor (TNF) or interleukin-17 (IL-17). Response rates for both are similar with the target of treatment achieved in approximately 50% of patients; however, response cannot currently be predicted. OPTIMISE tests whether a patient's blood results can help predict which biologic is more likely to illicit a response.

This section will only report primary and secondary objectives that are covered by this SAP. Exploratory objectives are addressed by industry collaborators as described in the protocol and are not covered here.

Primary Objective:
To compare the response in participants to see whether it differs according to baseline CD4 T cell activated Th17 levels, on the clinical response to TNF and IL-17A inhibitor therapy in PsA.

Secondary Objectives:

1. To compare the response in participants to see whether it differs according to intracellular IL-17 levels, on the clinical response to TNF and IL-17A inhibitor therapy in PsA.
2. To understand if the activated Th17 surface and intracellular IL-17 levels resolves after treatment with IL-17A blockade and how it is altered after TNF blockade.
3. To understand if changes in the activated Th17 surface and intracellular IL-17 levels differ in treatment responders and non-responders.
4. To explore if activated Th17 surface and intracellular IL-17 levels are associated with response in different PsA tissues.
5. To explore if activated Th17 surface and intracellular IL-17 levels are associated with response and disease impact from the patients' perspective

The estimand for the primary objective (including the analysis of the primary outcome) is described in Table 1.

Table 1: Estimand-to-analysis table template

Primary Objective: To compare the response in participants to see whether it differs according to baseline CD4 T cell activated Th17 levels on the clinical response to TNF and IL-17A inhibitor therapy in PsA.	
Estimand: The interaction effect of baseline CD4 T cell activated Th17 proportion with biologic treatment (TNF or IL-17A inhibitor therapy) on minimal disease activity (MDA) in adults aged over 18 years with psoriatic arthritis who are planning to start biologic therapy for their psoriatic arthritis, 6 months after initiating either TNF or IL-17A inhibitor therapy.	
Treatment: TNF inhibitor (adalimumab) IL-17A inhibitor (secukinumab) Both are currently first line biologic treatments for PsA. Following the screening visit and subsequent randomisation, patients will receive either a TNF or IL-17A inhibitor according to the randomisation allocation. These will be given open label at the usual licensed dose and patients will be taught to self-administer the treatments as in usual NHS practice.	
Estimand	**Analysis**
Target population The population targeted are adults (≥18 years old) with psoriatic arthritis confirmed by the CASPAR criteria who are planning to start biologic therapy for their PsA following routine clinical practice, who have no contraindications to a biologic therapy.	**Analysis set** All randomised participants who met the eligibility criteria will be analysed according to the treatments allocated. **Sensitivity analysis:** The same analysis approach will be applied to a Per-Protocol (PP) analysis set.
Outcome Minimal disease activity (MDA) criteria at 3 months post-treatment initiation.	**Outcome definition** MDA, the primary clinical response outcome, is defined as a dichotomous composite criteria including clinical outcomes (tender joint count, swollen joint count, enthesitis count and psoriasis score) and patient reported outcomes (patient global activity score, patient pain score and function measured by the HAQ). The assessment of MDA is detailed in section 3.7.
Handling of intercurrent events The primary analysis targets a treatment policy estimand. A treatment policy estimand will be applied to the calculation of MDA for the following intercurrent events:	**Handling of missing data** The primary approach used assumes that the missing data is missing at random (MAR) conditional on all the other data collected used. It is intended that analysis will be conducted on all available data, but the nature and pattern of missingness will be carefully considered and documented. Various

• a participant receives a different treatment to that which they were randomised to, • a participant receives no treatment or misses a dose • a participant ceases the treatment they were randomised.	analysis methods to explore and handle missing data will be explored if deemed appropriate.
Population-level summary measure	**Analysis approach**
Interaction effect of the treatment by biomarker (Th17) interaction.	Odds Ratios of the interaction effect between the biomarker (baseline Th17 proportion) and treatment (with 95% confidence interval, CI) and p values estimated using mixed effects logistic regression model. The model will regress Minimal Disease Activity (MDA) on Th17 as a continuous indicator, randomised treatment and an interaction between Th17 and randomised treatment. The model will adjust for the stratification factor, psoriasis severity (PASI, included as a continuous covariate) as a fixed effect. Study centre will be included as a random effect. The primary focus is on the interaction between biomarker and treatment. Further details are provided below in section 6.1, 6.2.

[1]Strategies defined in E9 (R1) include treatment policy, while on treatment, principal stratum and hypothetical

3. STUDY METHODS

3.1 Trial Design/framework

OPTIMISE is a phase III, open-label multi-centre, parallel-group, two arm randomised controlled study with a focus on the interaction between a biomarker and treatment (biomarker stratified design).

3.2 Randomisation and Blinding

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

Full details of the randomisation are available in the OPTIMISE Randomisation and Blinding Plan (Version 1.0 - 01Jul2021), stored in the confidential statistical section of the TMF.

There is no blinding of treatment allocation, so no allocation code or code-breaking procedure is required. All relevant study personnel will be informed of the treatment allocation by email. However, site staff will be unaware of activated Th17 level.

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

3.3 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 [1,2,3] 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 around 50%.

Sample Size Calculation
Please refer to the protocol [1] and published protocol paper [2] for the initial sample size calculation (using the biomarker Th17 as a categorical variable with two levels).

The sample size calculation was then updated after the trial opened for recruitment to allow using Th17 as a continuous outcome, assuming a biomarker by treatment interaction effect of 0.2, a type-I error rate of 0.05, and 90% power. This calculation also 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. Under these assumptions, a simulated sample size produced in R (Version 4.2.1), and using the {InteractionPoweR} [3,4] package using 10,000 simulated iterations produced a required sample size of 240 participants (120 per group), which, including a loss-to-follow-up of 10%, translates to a required recruitment of 134 participants per group (268 in total).

3.4 Statistical Interim Analysis, Data Review and Stopping guidelines

A Data and Safety Monitoring Committee oversees the conduct of the trial and safety of participants by reviewing recruitment and follow-up.

No formal interim analysis or early stopping rules are planned.

3.5 Timing of Analysis

The analysis of all trial outcomes will be conducted allowing for the appropriate time required to clean and prepare the data for all final analyses.

3.6 Blinded analysis

A blinded analysis of data (data analysed with no treatment information added) will be undertaken prior to the final data lock to enable data cleaning and raise data queries.

3.7 Statistical Analysis Outline

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

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

Standard descriptive statistics will be used to describe the demographics between the treatment groups reporting means and standard deviations or medians and interquartile ranges as appropriate for continuous variables and numbers and percentages for binary and categorical variables. All comparative outcomes will be presented as summary statistics and reported together with 95% confidence intervals.

All analyses will be carried out under a treatment policy strategy.

The primary analysis will be a mixed effects logistic regression mixed effects model adjusted for Th17 proportion as a continuous variable (0 – 100, %), treatment arm (TNF/IL-17A inhibitor therapy), an interaction between Th17 proportion and treatment arm, and randomisation stratification variables (psoriasis severity as a continuous variable (0 -72), and participant study centre as a random effect Primary focus is on the interaction between biomarker and treatment.

It is intended that analysis will be conducted on all available data, but the nature and pattern of missingness will be carefully considered and documented. Various analysis methods to explore and handle missing data will be explored if deemed appropriate.

For both the main analysis of the primary outcome under the primary comparison and any related analyses, models will be simplified (e.g. grouping small sites) if there are issues with convergence/parameter estimation.

It is anticipated that all statistical analyses will be undertaken using Stata (Release 17, College Station, TX: StataCorp LLC, www.stata.com) and/or R (Version 4.5.3, [5]).

4. STATISTICAL PRINCIPLES

4.1 Statistical Significance and Multiple Testing

There is no correction for multiple testing. The significance level used will be 0.05 and 95% confidence intervals will be reported. All secondary analyses will be considered as supporting the primary analysis and will also be analysed using a significance level of 0.05 with 95% confidence intervals (CI).

4.2 Definition of Analysis Populations

Intention to treat (ITT): inclusion of all available randomised participants who will be analysed in the groups to which they were randomised to irrespective of compliance.

Per-Protocol (PP): eligible participants, without important intervention protocol deviations, who were still taking their allocated intervention up to the end of the study follow-up period (24 weeks) will be analysed according to the treatment they were allocated to. Participants who were lost to follow-up or withdrew or otherwise had missing treatment compliance data up to 24 weeks will be excluded from this analysis population since it will not be possible to determine their treatment compliance up to the end of the follow-up period.

5. TRIAL POPULATION AND DESCRIPTIVE ANALYSES

5.1 Representativeness of Study Sample and Patient Throughput

The flow of participants through each stage of the trial, including the number of individuals approached, screened, randomised to each group, receiving allocated treatment, and included in the primary analysis will be summarised using a CONSORT flow chart. Reasons for ineligibility, loss to follow-up and exclusion from the primary analysis will be summarised. See the SAP Data Definitions and Tables for an illustrative example of a CONSORT diagram for the trial.

5.2 Withdrawal from treatment and/or follow-up

It is likely that some data may not be available due to voluntary withdrawal of participants, lack of completion of individual data items or general loss to follow-up. Where possible the reasons for missing data will be ascertained and reported.

Withdrawals/loss to follow-up together with reasons will be reported by intervention arm . Any deaths (and their causes) will be reported separately.

5.3 Baseline Characteristics

Numbers (with percentages) for binary and categorical variables and mean (and standard deviation), or median (with lower and upper quartiles) for continuous variables will be presented; there will be no tests of statistical significance nor confidence intervals for differences between randomised groups on any baseline variable.

5.4 Unblinding

The only concealment in the OPTIMISE trial is for recruiting centre staff who will be unable to know a participant's Th17 level.

5.5 Treatment Compliance with Details of Intervention

The compliance with randomised treatment will be reported by randomised group. Participants who stopped taking their randomised medication along with reasons and what other therapy has been started will be reported.

5.6 Reliability

To ensure consistency, validation checks of the data will be conducted. This will include checking for duplicate records, checking the range of variable values and validating potential outliers where possible (referring back to sites if necessary). As the data is collected electronically, many of these checks will be implemented automatically as part of the data entry procedure and data collection instruments have been validated prior to data entry commencing.

For each variable, missing value codes will be checked for consistency.

6. ANALYSIS

6.1 Outcome Definitions

Primary outcome measure: Minimal Disease Activity (MDA) at 24 weeks post-randomisation.

Secondary outcome measures:

Measured at 12 weeks (TNF Inhibitor group only) or 16 weeks (IL-17A Inhibitor group only) and 24 weeks post-randomisation:

- MDA
  - Tender Joint Counts
  - Swollen Joint Counts
  - Enthesitis (Total Enthesitis count)
  - Psoriasis (PASI)
  - Patient pain VAS
  - Global Disease Activity (Patient Global VAS)
  - HAQ
- PASDAS
  - Physician Global VAS
  - Global Disease Activity (Patient Global VAS)
  - Tender Joint Counts
  - Swollen Joint Counts
  - SF36-PCS
  - Leeds Enthesitis Count
  - Tender Dactylitis Count
  - CRP
- PsAID
- SF36
- WPAI

Full details of all scores and their derivations (where necessary) are found in the SAP Data Definitions and Tables.

6.2 Analysis Methods

This section describes the analysis methods for the primary and secondary objectives.

Primary outcome

The primary focus of the study is on the interaction effect between baseline CD4 T cell activated Th17 proportion (biomarker) and treatment on MDA at 24 weeks.

This interaction effect will be estimated using a multivariable logistic mixed effects model. The model will regress MDA at 24 weeks on treatment, baseline Th17, a treatment by baseline Th17 interaction term, and adjust for randomisation stratification variables (PASI as a continuous variable, and participant study centre (as a random effect). The estimated odds ratio for the interaction term with 95% confidence intervals and p-value will be reported. Plots of the distribution of the biomarker will also be reported.

Secondary Outcomes

Secondary objective 1: To compare the response (MDA) in participants to see whether it differs according to intracellular IL-17 levels on the clinical response to TNF and IL17A inhibitor therapy in PsA.

This objective aims to estimate the interaction effect between baseline IL-17 and treatment on MDA at 12/16 weeks and 24 weeks.

This interaction effect will be estimated using a multivariable logistic repeated measures mixed effects model will be fitted. The model will regress MDA (collected at 12 and 24 weeks for participants allocated to TNF and at 16 and 24 weeks for participants allocated to IL-17A) on treatment, baseline IL-17, a treatment by IL-17 interaction term, time, a treatment by time interaction term, and adjust for randomisation stratification variables (PASI as a continuous variable, baseline Th17 as a continuous variable, and participant study centre as a random effect. The estimated odds ratio for the interaction term will be reported at 12/16 weeks and at 24 weeks. 95% confidence intervals and p-value will also be reported at the corresponding timepoints.

Secondary objective 2: To understand if the activated Th17 surface and intracellular IL-17 levels resolves after treatment with IL-17A blockade and how it is altered after TNF blockade.

This objective aims to estimate the interaction effect between baseline Th17 and treatment on IL-17 at 24 weeks.

This effect will be estimated using a multivariable linear mixed effects model. The model will regress IL-17 at 24 weeks on treatment, baseline Th17, a treatment by Th17 interaction term, and adjust for baseline IL-17, and randomisation stratification variables (PASI as a continuous variable, and participant study centre as a random effect). The estimated interaction effect will be reported at 24 weeks with 95% confidence intervals and p-value.

Secondary objective 3: To understand if changes in the activated Th17 surface and intracellular IL-17 levels differ in treatment responders and non-responders (measured with MDA).

This objective aims to estimate two associations:

1. The association between the change in Th17 (between baseline and 4 weeks) on MDA at 24 weeks.

   This effect will be estimated using a multivariable logistic mixed effects model. The model will regress MDA at 24 weeks on the change in Th17 between baseline and 4 weeks, and adjust for treatment, baseline MDA and randomisation stratification variables (PASI as a continuous variable, baseline Th17 as a continuous variable, and participant study centre as a random effect). The estimated odds ratio for a 1% increase in change in Th17 on MDA at 24 weeks will be presented. 95% confidence intervals and p-value will also be reported.

2. The association between the change in IL-17 (between baseline and 4 weeks) on MDA at 24 weeks.

   This effect will be estimated using a multivariable logistic mixed effects model. The model will regress MDA at 24 weeks on the change in IL-17 between baseline and 4 weeks, and adjust for treatment, baseline MDA and randomisation stratification variables (PASI as a continuous variable, baseline Th17 as a continuous variable, and participant study centre as a random effect). The estimated odds ratio of the interaction effect at 24 weeks will be presented. 95% confidence intervals and p-value will also be reported.

Secondary objective 4: To explore if activated Th17 surface and intracellular IL-17 levels are associated with response (PASDAS) in different PsA tissues.

This objective aims to estimate the following key effects on PASDAS:
Note: PASDAS is collected and analysed at 12 and 24 weeks for participants allocated to TNF and at 16 and 24 weeks for participants allocated to IL-17A

1. The interaction effect between baseline Th17 and treatment on PASDAS at 12/16 weeks and 24 weeks.

   This effect will be estimated using a multivariable linear repeated measures mixed effects model. The model will regress PASDAS on treatment, baseline Th17, a treatment by Th17 interaction term, time, a treatment by time interaction term, and adjust for baseline PASDAS and randomisation stratification variables (PASI as a continuous variable, and participant study centre as a random effect). The interaction effect with 95% confidence intervals and p-values will be reported at 12/16 weeks and 24 weeks.

2. The interaction effect between baseline IL-17 and treatment on PASDAS at 12/16 weeks and 24 weeks.

   This effect will be estimated using a multivariable linear repeated measures mixed effects model. The model will regress PASDAS on treatment, baseline IL-17, a treatment by IL-17 interaction term, time, a treatment by time interaction term, and adjust for baseline PASDAS and randomisation stratification variables (PASI as a continuous variable, and participant study centre as a random effect). The interaction effect with 95% confidence intervals and p-values will be reported 12/16 weeks and 24 weeks.

Secondary objective 5: To explore if activated Th17 surface and intracellular IL-17 levels are associated with response (PsAID, SF36, WPAI) and disease impact from the patients' perspective.

This objective aims to estimate the following key effects:
Note: PsAID, SF36 and WPAI are collected and analysed at 12 and 24 weeks for participants allocated to TNF and at 16 and 24 weeks for participants allocated to IL-17A

1. The interaction effect between baseline Th17 and treatment on PsAID at 12/16 weeks and 24 weeks.

   This effect will be estimated using a multivariable linear repeated measures mixed effects model. The model will regress PsAID on treatment, baseline Th17, a treatment by Th17 interaction term, time, a treatment by time interaction term, and adjust for baseline PsAID and randomisation stratification variables (PASI as a continuous variable, and participant study centre as a random effect). The interaction effect with 95% confidence intervals and p-value will be reported at 12/16 weeks and 24 weeks.

2. The interaction effect between baseline IL-17 and treatment on PsAID at 12/16 weeks and 24 weeks.

   This effect will be estimated using a multivariable linear repeated measures mixed effects model. The model will regress PsAID on treatment, baseline IL-17, a treatment by IL-17 interaction term, time, a treatment by time interaction term, and adjust for treatment,

baseline PsAID and randomisation stratification variables (PASI as a continuous variable, baseline Th17 as a continuous variable and participant study centre as a random effect). The interaction effect with 95% confidence intervals and p-value will be reported at 12/16 weeks and 24 weeks.

3. The interaction effect between baseline Th17 and treatment on SF36 at 12/16 weeks and 24 weeks.

   This effect will be estimated using a multivariable linear repeated measures mixed effects model. The model will regress SF36 on treatment, baseline Th17, a treatment by baseline Th17 interaction term, time, a treatment by time interaction term, and adjust for baseline SF36 and randomisation stratification variables (PASI as a continuous variable, and participant study centre as a random effect). The interaction effect with 95% confidence intervals and p-value will be reported at 12/16 weeks and 24 weeks.

4. The interaction effect between baseline IL-17 and treatment on SF36 at 12/16 weeks and 24 weeks.

   This effect will be estimated using a multivariable linear repeated measures mixed effects model. The model will regress SF36 on treatment, baseline IL-17, a treatment by baseline IL-17 interaction term, time, a treatment by time interaction term, and adjust for treatment, baseline SF36 and randomisation stratification variables (PASI as a continuous variable, baseline Th17 as a continuous variable and participant study centre as a random effect). The interaction effect with 95% confidence intervals and p-value will be reported at 12/16 weeks and 24 weeks.

WPAI will also be descriptively presented with means and standard deviation at each timepoint by arm and by baseline dichotomous Th17 and IL-17 groups (defined as ≤ median of corresponding biomarker and >median of corresponding biomarker).

6.3 Missing Data

Proportion of missing values per variable will be presented. Patterns of missing data will be explored

It is intended that analysis will be conducted on all available data, but the nature and pattern of missingness will be carefully considered and documented. If it is plausible that the data is missing not at random, a search for baseline factors not included in the primary analysis model which explain missingness will be performed and if variables are found and deemed appropriate, they will be used as further adjustment variables to the primary analysis model as a sensitivity analysis. If no variables are identified, no further missing data analysis will be performed. Various analysis methods to explore and handle missing data will be explored if deemed appropriate.

Reasons for ineligibility, non-compliance, withdrawal or other protocol violations will be documented. Secondary analyses will be complete cases only, but missing data patterns will be explored.

6.4 Sensitivity Analysis

Supporting primary outcome analyses

The main primary analysis will also be conducted in the Per-Protocol population.

The primary analysis model will be additionally modelled using a restricted cubic spline on the interaction term to. A line plot of the probability of MDA across the baseline Th17 range by treatment

will be presented using this model's estimates. If the relationship between Th17 and MDA is suspected to be represented better with a restricted cubic spline, this model will also be used to present the estimated odds ratios (based on the model parameters) between TNF inhibitor and IL-17A inhibitor therapies at the 20th, 40th, 50th, 60th, and 80th percentiles of baseline Th17 proportions.

Given the two randomised treatments are established NHS treatments, a supporting analysis will be performed on the primary outcome of MDA at 24 weeks that utilises a simpler analysis model. This analysis model will be the same as the primary analysis model but will not include the study centre random effect. This model is pertinent as both treatments should be homogenous across the recruiting centres in a pragmatic trial so using a simpler model may yield a better-fit model. Model fit will be compared to the primary analysis model.

The cut-point for the Th17 level used in the randomisation process (≤/>1.58%) has been defined as it is the UK median. It is possible that the trial population will have a particularly unequal number of participants in the high and low groups. The MDA responses will be descriptively summarised by Th17 level, however with the cut point defined as the Th17 sample median (low: ≤ Th17 sample median, high: > Th17 sample median).

The association between baseline Th17 and baseline IL-17 will also be explored graphically.

6.5 Pre-specified Subgroup Analysis

No subgroup analyses are planned as part of this analysis plan.

6.6 Supplementary/ Additional Analyses and Outcomes

No additional analyses are planned as part of this analysis plan.

6.7 Harms

Serious adverse events will be reported by treatment group and Th17 level along with causality, expectedness and details of each event.

7. VALIDATION OF THE PRIMARY ANALYSIS

To validate the primary outcome and key secondary outcomes (MDA at 24 weeks and PASDAS at 24 weeks), a statistician not involved in the trial will repeat the analyses detailed in this SAP, by using different statistical software (if possible). The results will be compared and any unresolved discrepancies will be reported in the Statistical report (See OCTRU SOP STATS-005 Statistical Report). Both MDA and PASDAS require derivation. These derivations will need to be performed by the second statistician to ensure they have been performed correctly.

8. SPECIFICATION OF STATISTICAL PACKAGES

All analysis will be carried out using appropriate validated statistical software such as STATA, SAS, SPLUS or R. The relevant package and version number will be recorded in the Statistical report.

9. PUBLICATION

This study will be conducted as part of the portfolio of trials in the registered UKCRC Oxford Clinical Trials Research Unit (OCTRU) at the University of Oxford. It will follow their Standard Operating Procedures ensuring compliance with the principles of Good Clinical Practice and the Declaration of Helsinki and any applicable regulatory requirements.

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APPENDIX: GLOSSARY OF ABBREVIATIONS

CI	Chief Investigator
DSMC	Data and Safety Monitoring Committee
HEAP	Health Economic Analysis Plan
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SUSAR	Serious Unexpected Adverse Reaction
TSC	Trial Steering Committee
MDA	Minimal Disease Activity
PASDAS	Psoriatic Arthritis Disease Activity Score