SPEED

Clinical effectiveness of standard step up care (methotrexate) compared to early combination DMARD therapy with standard step up care compared to early use of TNF inhibitors with standard step up care for the treatment of Moderate to Severe Psoriatic arthritis: a 3-arm parallel group randomised controlled trial.

Statistical Analysis Plan

Version 1.0 – 10Dec2024

Linked to SAP - Data definitions and Tables
Version 1.0_10Dec2024

Based on Protocol version 11.2 – 17Apr2023

Trial registration:

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

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1. INTRODUCTION

This document details the proposed data presentation and analysis for the main paper(s) and final study reports from the **National Institute for Health Research (NIHR)-funded Multicentre Randomised Controlled Trial comparing early combination DMARD therapy with standard step up care compared to early use of TNF inhibitors with standard step up care for the treatment of Moderate to Severe Psoriatic arthritis (SPEED).** The results reported in these papers should follow the strategy set out here. Subsequent analyses of a more exploratory nature or of extended study follow-up 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. These two documents should be read in tandem.

1.1 Key personnel

List of key people involved in the drafting and reviewing this SAP, together with their role in the trial and their contact details.

Author(s) (Trial statistician)

Trial statistician: Elnaz Saeedi **elnaz.saeedi@ndorms.ox.ac.uk**

Reviewers (e.g. Trial Manager, DSMC, TSC, Statistician as appropriate)

Lead Statistician: Sofia Massa **sofia.massa@ndorms.ox.ac.uk**

Chief Investigator: Laura Coates **laura.coates@ndorms.ox.ac.uk**

Approver (Senior Statistician, Chief Investigator)

Lead Statistician: Sofia Massa **sofia.massa@ndorms.ox.ac.uk**

Chief Investigator: Laura Coates **laura.coates@ndorms.ox.ac.uk**

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_10Nov2024		Protocol_V11.2_17Apr2023	Not applicable as this is the 1st issue

2. BACKGROUND AND OBJECTIVES

The aim of the SPEED (Severe Psoriatic arthritis – Early intervEntion to control Disease) trial is to compare outcomes in PsA patients with poor prognostic factors treated with standard step-up csDMARDs, combination csDMARDs or a course of early biologics. This is three arms open label RCT within a TWiCs cohort (Monitor-PsA REC Ref 17/SC/0556). Patients with newly diagnosed PsA and at least one poor prognostic factor (polyarthritis, CRP>5mg/dL, HAQ >1, radiographic erosions) are randomised 1:1:1 to either standard care with 'step up' csDMARD therapy, initial therapy with combination csDMARDs (methotrexate with either sulfasalazine or leflunomide) or to early biologics induction therapy (adalimumab plus methotrexate). The primary outcome is the PsA disease activity score (PASDAS) at week 24.

The secondary objectives will explore the speed of response using PASDAS and time to achieve minimal disease activity (MDA) criteria, longer term response at 48 weeks and impact on quality of life. Our Exploratory objectives include domain specific responses (e.g. reduction in skin psoriasis, enthesitis, dactylitis), quality of life, treatment satisfaction, safety and radiographic change.

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 initial effectiveness of early combination DMARD therapy (arm 2) and early use of TNF inhibitors (arm 3) with standard step up care (received in the TWiCs cohort, arm 1) at 24 weeks.
Estimand: A single primary estimand will assess the difference in PASDAS scores (Psoriatic Arthritis Disease Activity Score) at 24 weeks among patients with moderate/severe Psoriatic Arthritis. The comparison will include those receiving standard step-up care (control), early combination DMARD therapy, and early TNF inhibitor therapy. The estimand considers patients irrespective of their adherence to the assigned intervention, unforeseen technical difficulties, or deviations, including receiving other standard care interventions necessary during the trial.
Treatment: Combination DMARD therapy (arm 2), early use of TNF inhibitors (arm 3), standard step up care (arm 1).

Estimand	*Analysis*
Target population	***Analysis set***
Participants with newly diagnosed PsA who have not previously received treatment with any DMARDs for their articular disease. Only participants with moderate/severe disease defined as those with poor prognostic baseline factors will be eligible.	Participants have consented to the MONITOR-PsA cohort and to be approached for alternate interventional therapies. Presence of ≥1 poor prognostic factor at baseline (polyarticular disease with ≥5 active joints at baseline, raised C reactive protein, radiographic damage, health assessment questionnaire>1) Participant has clinically acceptable laboratory results • Haemoglobin count > 8.5 g/dL • White blood count (WBC) > 3.5 x 109/L • Absolute neutrophil count (ANC) > 1.5 x 109/L • Platelet count > 100 x 109/L • AST or ALT and alkaline phosphatase levels <3 x upper limit of normal
Variable	***Outcome measure***
Data collected from all participants will be entered within the cohort study (MONITOR-PsA) data recording systems. The data consists of clinical assessments, patient reported outcome measures (PROM) questionnaires and documentation of routine efficacy and safety blood tests.	PsA disease activity score (PASDAS) score[10] (on a continuous scale) at 24 weeks.
Handling of intercurrent events	***Handling of missing data***
Switching Treatment arm: Participants who receive a different intervention to that which they were allocated will be analysed according to their randomised allocation The intercurrent event will be handled under a treatment-policy strategy.	Multilevel modelling of outcome scores over time, imputes implicitly intermittent missing data over the post-randomisation period of follow-up. The underlying assumption is missing at random (MAR) conditional on all other outcome scores and minimisation factors. This is the main approach to handling missing data. *Sensitivity analysis:* PASDAS score will be imputed for any individual with three or less components of PASDAS missing. Multiple imputation by chained equations will be used.
Population-level summary measure	***Analysis approach***
	Hierarchical testing strategy with initial gatekeeping test (initial global test and if null hypothesis of the global test is rejected at the 0.05 level, further tests will be carried out).

Average Treatment effect (ATE): Mean difference in PASDAS scores at 24 months, between each of the pairwise comparisons.	The primary outcome, PASDAS score at 24 weeks, will be analysed using mixed effects linear models and estimates for the difference between groups will be presented with the corresponding 95% confidence intervals. Additional analyses will be undertaken using mixed effects linear models (for continuous outcomes) or mixed effect logistic models (for binary outcomes) adjusting for randomisation factors and baseline scores. *Sensitivity analyses:* Multiple imputation via chained equations for the PASDAS score.

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

3. STUDY METHODS

3.1 Trial Design/framework

This is a randomised superiority open-label trial assessing the effectiveness of more intensive drug therapy within a treat to target regime in moderate/severe PsA within a cohort in a "Trials within Cohorts" (TWiCs) design. Participants in the cohort may be offered interventional trials with other members of the cohort acting as comparative controls where they have consented to this. A total of 315 participants will be recruited (105 to the cohort as controls and 210 receiving the interventions: 105 in arm 2 and 105 in arm 3). Each participant will be followed for 48 weeks within this trial and will then revert to standard care within the cohort.

3.2 Randomisation and Blinding

Randomisation (1:1:1) to the interventions is undertaken via a centralised randomisation service run through the Oxford Clinical Trials Research Unit (OCTRU). Computer-generated randomisation allocations using a minimisation approach including a random element l ensure balanced allocations across the treatment groups. The following minimisation factors are used:

- Recruiting trial site
- Polyarticular (≥5 active joints) vs oligoarticular (<5 active joints)
- Duration of disease prior to diagnosis (<12 months, ≥12 months)

The first 30 participants are randomised using simple randomisation to seed the minimisation algorithm which will have probabilistic element of 0.8 introduced to ensure unpredictability of the treatment assignment. The treatment received is open label so there is no necessity for code breaking. Specialist nurses will undertaking joint assessment blinded.

Full details of the randomisation are available in SPEED_RBP_V1.0_25Sep2018, stored in the confidential statistical section of the TMF.

3.3 Sample Size

The primary outcome is PASDAS (continuous outcome) at 24 weeks. The primary null hypothesis is a global assessment that there is no difference between all three treatment arms.

This study was originally powered for a PASDAS good response (binary outcome) using data from TICOPA to inform the likely response of the step up cohort control arm. Assuming 30% of participants in the control arm

achieve the Response (defined as "good" PASDAS response only) with 80% power and 5% significance and allowing for 10% loss to follow-up 315 (105 per arm) would be required to detect a difference of 20%, i.e. that 50% achieve a PASDAS good response in the active arms by 6 months.

Following a review of the sample size following slower than expected recruitment (partly due to the COVID-19 pandemic) has resulted in a change to the way the primary outcome is specified – using the PASDAS score on the continuous scale rather than as a binary outcome of those achieving a good response.
Based on the assumptions of 80% power, 5% two-sided statistical significance to detect a minimally clinically important difference (MCID) of 0.8 on the PASDAS continuous scale with a standard deviation of 1.5, and allowing for 10% loss to follow-up, an updated target sample size of 192 participants (64 per arm) is required. The MCID was developed after the SPEED trial commenced and is reported in Mulder et al 2022. The standard deviation is based on the observed variability in the continuous PASDAS in the MONITOR cohort.

3.4 Statistical Interim Analysis, Data Review and Stopping guidelines

No formal interim analyses, and formal statistical testing are planned to take place prior to the final analysis.

3.5 Timing of Analysis

The trial analysis will take place after all participants have completed their follow-up. No interim analyses are planned.

3.6 Blinded analysis

Blinded analyses may be carried out prior to the final analysis, for data cleaning purposes .

4. STATISTICAL PRINCIPLES

4.1 Statistical Significance and Multiple Testing

Statistical significance will be set at 5% significance (with no adjustment for multiple testing). All comparative outcomes will be presented as summary statistics with 95% confidence intervals and reported in accordance with the CONSORT Statement and its appropriate extensions (http://www.consort-statement.org/consort-2010).
Secondary endpoints will be used to further inform the primary endpoint, and for hypothesis generation hence there is no adjustment for multiple testing.

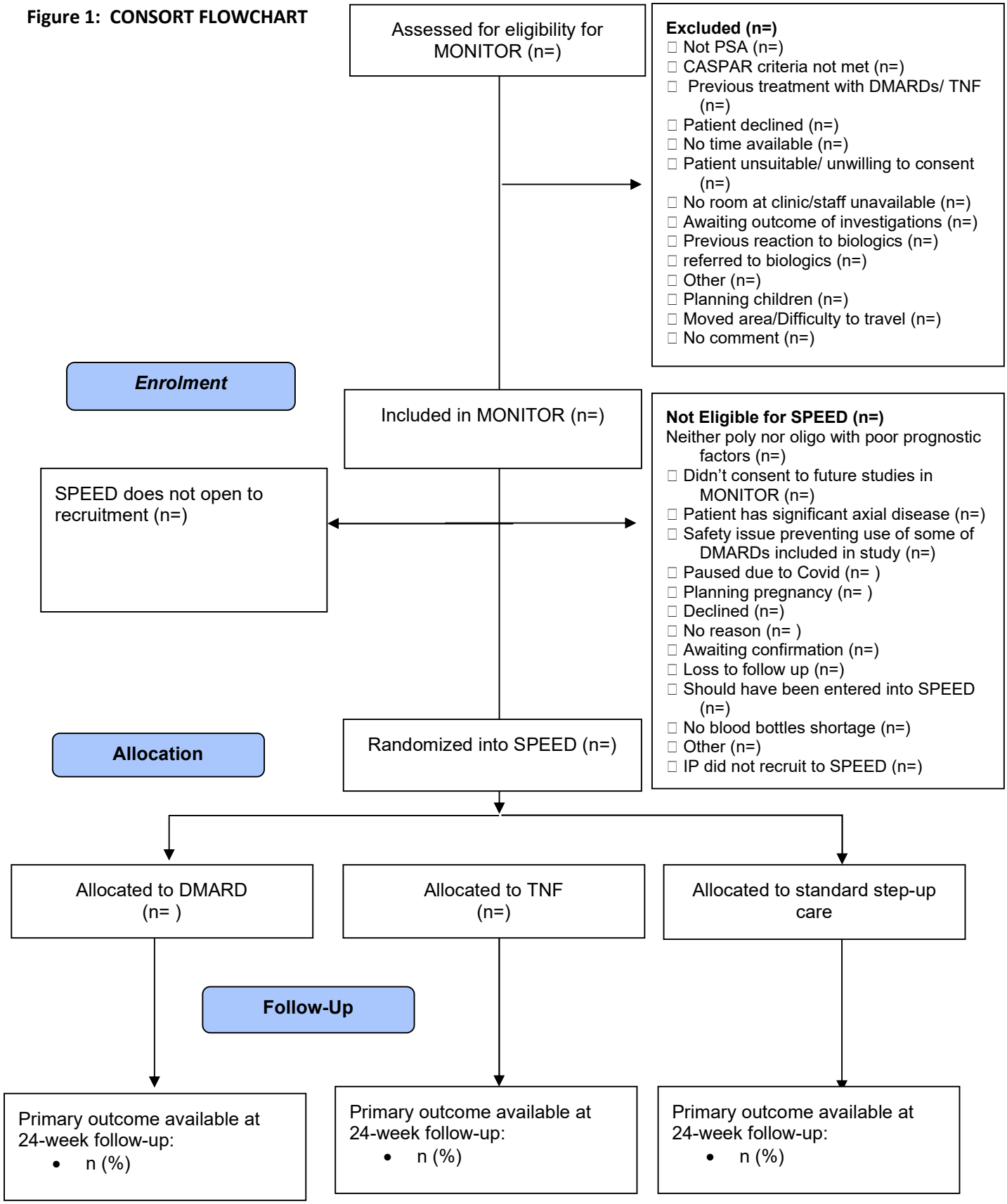
4.2 Definition of Analysis Populations

The intention to treat population will include those who have been offered the treatment interventions or those randomised to stay in the cohort as controls, regardless of whether they accepted the treatment or received the intervention. Participants will be analysed based on their randomised groups.
The per–protocol population will include those who received their randomised treatment and exclude participants who have been major protocol violators as defined in the statistical analysis plan.

5. TRIAL POPULATION AND DESCRIPTIVE ANALYSES

5.1 Representativeness of Study Sample and Patient Throughput

Figure 1: CONSORT FLOWCHART



5.2 Withdrawal from treatment and/or follow-up

Each participant has the right to withdraw from treatment or completely from the trial at any time, with data collected up to the point of withdrawal retained and used in the analysis as stated in the PIS. If appropriate they may remain in the cohort study unless they wish to be withdrawn from MONITOR as well.
In addition, the Investigator may discontinue a participant from treatment within the trial at any time if the Investigator considers it necessary for any reason presented in Table 2.
If the participant or investigator withdraws from active treatment, participants will still be asked to complete follow up with data collected at planned time points, unless they indicate that they wish to withdraw from follow-up.
Withdrawn participants will not be replaced. The reason for withdrawal, where provided, will be recorded in the Case Report Form (CRF). If the participant is withdrawn from treatment due to an adverse event, the investigator will arrange for additional follow-up visits or telephone calls as required until the adverse event has resolved or stabilised.

Table 2: Withdrawals by intervention group

Reason for Withdrawal	**Step-up care N (%)**	**DMARD N (%)**	**TNF N (%)**	**Total N (%)**
Pregnancy				
Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)				
Significant non-compliance with treatment regimen or trial requirements				
An adverse event which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures				
Disease progression which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures				
Withdrawal of Consent				
Loss to follow up				

5.3 Baseline Characteristics

Baseline characteristics will be reported by treatment group, including the stratification/minimisation factors and important prognostic, demographic and clinical covariates.

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. Refer to Table 2 in the SPEED SAP DD&T document.

5.4 Unblinding

This is not a blinded trial.

5.5 Treatment Compliance with Details of Intervention

Non-compliance is assessed at each clinical trial visit and any missed doses reported by the participants are recorded. This data is stored in the medication data. A binary variable called "adherence" is available for each individual at Weeks 12, 24, 36, 48. For each of these timepoints the number (%) of compliant individuals will be reported.
A CACE analysis will only be reported for the Week 24 timepoint (the primary outcome timepoint).

5.6 Reliability

Most of the data is entered directly by participants or clinicians onto LimeSurvey and will be directly transferred onto the trial database (OpenClinica). Therefore, no source data verifications can be performed on the patient reported outcomes.
Data transfer and validation of the formula used on the database have been performed prior to the start of the trial and have been found to work reliably.
Additional calculations, such as for PROMs score, will be validated as part of the planned analyses (including DSMC reports).

6. ANALYSIS

The statistical methods to be used to compare groups for primary and secondary outcomes and methods for point and interval estimation are summarised below. This includes methods for additional analyses, such as adjusted analyses and subgroup analyses.

6.1 Outcome Definitions

The primary outcome is the PASDAS score at 24 weeks. The PASDAS formula is calculated using a combination of clinician and patient reported items as follows:

PASDAS= ((0.18 √physician global VAS) + (0.159 √patient global VAS) – (0.253 x √SF36-PCS) + (0.101 x ln (SJC+1)) + (0.048 x ln (TJC+1)) + (0.23 x ln (LEI +1)) + (0.37 ln (tender dactylitis count+1)) + (0.102 x ln (CRP+1)) +2) x 1.5,

where ln is natural logarithm, PCS is the physical component summary scale of the Short Form-36, CRP is the C-reactive protein in mg/l. All VAS scores are 0–100 mm, Leeds Enthesitis Count ranges from 0–6; dactylitis count is the tender dactylitis count with a score range of 0–20. The joint count used is the 68 (tender) and 66 (swollen) joint count. The PASDAS score range is 0 to 10, with higher values indicating worse disease activity.

In addition, we will report the proportion of patients achieving a PASDAS good response and moderate response at week 24 and week 48. A PASDAS good response is defined as a reduction in PASDAS from baseline greater or equal than 1.6 and a final PASDAS score of less or equal than 3.2 as shown in the table below. A PASDAS moderate response is as detailed below.
The Final PASDAS score is the PASDAS score calculated at Week 24 (48, respectively). The improvement in PASDAS score is the difference between the score at Week 24 (Week 48, respectively) and baseline.

	Improvement in PASDAS score		
Final PASDAS score	≥1.6	<1.6 but ≥0.8	<0.8
≤3.2	Good	Moderate	Poor
>3.2 but <5.4	Moderate	Moderate	Poor
≥5.4	Moderate	Poor	Poor

Key secondary outcomes will include:

- Time from baseline to MDA response where MDA is defined as meeting 5 of the following 7 criteria: TJC ≤1; SJC ≤1; psoriasis activity and severity index (PASI) ≤1; patient pain visual analogue scale (VAS) ≤15mm; patient global VAS ≤20mm; health assessment questionnaire (HAQ) ≤0.5; tender enthesis points ≤1.
- PASDAS score (on a continuous scale) at 48 weeks.
- PASDAS good response and PASDAS moderate responses (as defined in the table below) at 24 and 48 weeks (see table 3).
- PSAID score (on a continuous scale) at 24 and 48 weeks.

6.2 Analysis Methods

A hierarchical method of testing will be used to compare the three treatment groups. This is a stepwise process where the first hypothesis must be rejected before moving on to the next and the process is completed when the hypothesis cannot be rejected.
Firstly, the three arms will all be compared in a global test with the primary null hypothesis that there is no difference between any of the means of the PASDAS score of the three treatment arms at week 24.
The global test will be performed via an Analysis of Variance (ANOVA) test, with PASDAS score as the dependent variable and the treatment as the independent variables.
If the variances of the three groups cannot be assumed the same, the approximate method of Welch (1951) will be used with the ANOVA test.
If all the assumptions of the ANOVA test do not hold then a Kruskal-Wallis non-parametric Analysis of Variance will be carried out.

If the global test null hypothesis is rejected at the 5% level, each intervention will be compared against the control step-up cohort with the following two null hypotheses:

1. There is no difference between the means of the PASDAS score of the early TNF inhibitor arm and the step-up cohort control arm at week 24.
2. There is no difference between the means of the PASDAS score of the early combination cDMARD arm and the step-up cohort control arm at week 24.

Both hypotheses will be tested at a 5% level of significance (with no adjustment for multiple testing). At this stage the t-test will be used (with equal or unequal variances depending on whether the assumptions of the t-test hold or not). If all the assumptions of the t-test do not hold then the Wilcoxon test will be used.

As an exploratory result, Dunnet test will be used to test both hypothesis as they both involve the same reference group (the step-up cohort control arm). Dunnett's test is a t-test with critical values adjusted for the correlation between the comparisons.
If both hypotheses are rejected at the 5% level, then the hypothesis of no difference between the mean PASDAS score of the two intervention arms will be tested.

The association between the primary outcome, PASDAS score at 24 weeks and the treatment groups will be analysed using linear mixed effect models. The models will be adjusted for stratification factors (centre as a random effect, arthritis subtype and symptom duration as fixed effects) and the baseline PASDAS score. Three

linear mixed models will be fitted: one for the comparison of the early combination DMARD with the standard step-up care, one for the comparison of the early TNF inhibitor arm and the standard step-up care and the last one to compare the DMARD arm with the TNF inhibitor. The adjusted estimates of the mean difference between each treatment group will be presented with the corresponding 95% confidence intervals.

Complier average causal effect (CACE) analysis[42] at 24 weeks will also be undertaken to take into account adherence to the randomised treatments for the primary outcome analysis. Non-compliance is assessed at each clinical trial visit and any missed doses reported by the participants are recorded.

Statistical analyses for key secondary endpoints collected at the follow-up assessments will include multilevel mixed-effects logistic or linear regression models for the binary or continuous outcomes, respectively. Models will be adjusted for baseline measures of the relevant outcome, as well as stratification factors and a time by treatment interaction term. Estimates of the mean difference between groups and 95% confidence intervals will be reported.

Time from baseline to MDA response will be compared across the three arms via Kaplan-Meier curves and the log-rank test.

A Cox proportional hazards model will estimate the hazard ratio (and confidence interval) of both the early combination cDMARD arm and the early TNF inhibitor arm versus the step-up cohort control arm. The Cox regression model will be adjusted for stratification factors. The proportional hazard assumption will be assessed graphically.

A further (exploratory) outcome will be progression in joint damage as measured by the modified Sharp-van der Heijde total and the erosion scores at 0 and 48 weeks. Means and standard deviations will be reported for both scores at the two timepoints above.

6.3 Missing Data

The number and percentage of individuals with missing data for each outcome at each time point will be summarised by intervention arm, along with reasons for missing-ness if known. Multilevel modelling of outcome scores over time, imputes implicitly intermittent missing data over the post-randomisation period of follow-up. The underlying assumption is missing at random (MAR) conditional on all other outcome scores and minimisation factors. This is the main approach to handling missing data.

6.4 Sensitivity Analysis

A sensitivity analysis will be carried out to assess the robustness of the findings of the primary outcome analysis. The continuous PASDAS score will be imputed using multiple imputation with chained equations for all individuals that have at least 5 components of the PASDAS score available (i.e., only three or less components missing). The imputation model will include all variables used in the analysis model. 100 datasets will be generated, and if the PASDAS score can be approximated by a normal distribution then a standard method of imputation will be used (regression or predictive mean matching).

6.5 Pre-specified Subgroup Analysis

No subgroup analyses are planned.

6.6 Supplementary/ Additional Analyses and Outcomes

No additional analyses are planned.

6.7 Health Economics and Cost Effectiveness (where applicable)

The statistician is not undertaking this analysis.

7. VALIDATION OF THE PRIMARY ANALYSIS

To validate the primary outcome and key secondary outcomes a statistician not involved in the trial analysis will independently repeat the analyses detailed in this SAP. This may be by using different statistical software. The results will be compared, and any unresolved discrepancies will be reported in the Statistical report (See OCTRU SOP STATS-005 Statistical Report).

8. SPECIFICATION OF STATISTICAL PACKAGES

All analysis will be carried out using appropriate validated statistical software, i.e. STATA or R. The relevant package(s) and version number(s) will be recorded in the Statistical report.

9. PUBLICATION

This study will be/has been 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/has followed their Standard Operating Procedures ensuring compliance with the principles of Good Clinical Practice and the Declaration of Helsinki and any applicable regulatory requirements.

10. REFERENCES

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Kang M, Kendall MA, Ribaudo H, Tierney C, Zheng L, Smeaton L, Lindsey JC. Incorporating estimands into clinical trial statistical analysis plans. Clin Trials. 2022 Jun;19(3):285-291. Doi: 10.1177/17407745221080463. Epub 2022 Mar 8. PMID: 35257600; PMCID: PMC9232859.

ICH E9(R1) Addendum on estimands and sensitivity analysis in clinical trials

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1. doi: 10.1186/2046-4053-4-1

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