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Original Research

The protocol of a clinical effectiveness trial comparing standard step-up care, early combination DMARD therapy and early use of TNF inhibitors for the treatment of moderate to severe psoriatic arthritis: the 3-arm parallel group SPEED randomized controlled trial

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Abstract

Objectives: The aim of the Severe Psoriatic arthritis – Early intervEntion to control Disease trial is to compare outcomes in psoriatic arthritis (PsA) patients with poor prognostic factors treated with standard step-up conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), combination csDMARDs or a course of early biologics.

Design: This multicentre UK trial was embedded within the MONITOR-PsA cohort, which uses a trial within cohort design.

Methods and analysis: Patients with newly diagnosed PsA and at least one poor prognostic factor (polyarthritis, C-reactive protein >5 mg/dL, health assessment questionnaire >1, radiographic erosions) were randomized equally and open-label 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 at week 24.

Ethics: Ethical approval for the study was granted by the South Central Research Ethics Committee (ref 18/SC/0107).

Discussion: Treatment recommendations for PsA suggest more intensive therapy for those with poor prognostic factors but there are no studies that have previously used prognostic factors to guide therapy. Applying initial intensive therapy has shown improved outcomes in other inflammatory arthritides but has never been tried in PsA. Combination csDMARDs have shown some superiority over single therapies but there are limited data and concerns about side effects. Early use of biologics has also been shown to be superior to methotrexate but these drugs are costly and not usually funded first line. However, if a short course of biologics can rapidly suppress inflammation allowing treatment to be withdrawn and response maintained on methotrexate, this may be a cost-effective model for early use.

Trial registration: ClinicalTrials.gov (NCT03739853) and EudraCT (2017-004542-24).

Keywords: biologics, clinical trial, polyarthritis, psoriatic arthritis

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Introduction

Psoriatic arthritis (PsA) is an inflammatory arthritis estimated to occur in 15% of people with psoriasis[1] affecting around 190,000 people in the UK.[2] Routine data sources across the UK have shown that 21.8% of patients diagnosed with new inflammatory arthritis have a diagnosis of PsA.[3] Two-thirds of people with PsA suffer progressive joint damage with associated increasing disability.[4,5] Both international treatment recommendations published by the European Alliance of Associations for Rheumatology and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis utilize a 'step-up' approach to treatment.[6,7] However, they suggest more intensive therapy for those with poor prognostic factors based on expert opinion. These factors (number of active joints, systemic inflammatory levels, baseline radiographic damage and poor function) are evidence based[8] but there are no studies that have previously used them to guide therapy.

Combinations of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), usually methotrexate with a second csDMARD, have been shown to have some advantages over single therapies in PsA[9] but there is limited evidence for this approach. A study of methotrexate with ciclosporin showed no clinical benefit with the combination, although there was some difference in disease control assessed by ultrasound.[9] The COMPLETE-PsA study compared methotrexate monotherapy with a combination of methotrexate and leflunomide in patients with PsA and found a benefit in PsA disease activity score (PASDAS[10]) reduction for the combination arm. However, treatment had to be discontinued due to side effects in 13 of 78 patients and the study only lasted for 16 weeks so longer-term outcome data are unavailable. These drugs would be affordable in most healthcare systems and are frequently prescribed in PsA but do raise concerns about patient tolerability and significant side effects.[11]

Early use of tumour necrosis factor (TNF) inhibitors has also been shown to be superior to methotrexate in head-to-head open-label trials[12–14] but there are no data on long-term outcomes. Some randomized controlled trials (RCTs) of TNF inhibitors in PsA have shown that the improvement in those initially receiving a placebo for 16–24 weeks before open-label therapy never catches up with those receiving TNF inhibitors from the start of the study, even at 1 and 2 years.[15] This suggests that earlier use of these therapies may improve long-term outcomes. However, these therapies are very expensive and unlikely to be funded for all patients as first-line therapy. If a 'remission induction' course of biologics, where patients receive a course of biologic treatment early in their treatment, can rapidly suppress inflammation allowing treatment to be withdrawn and response maintained on methotrexate then this may be a cost-effective model for early use. Applying initial intensive therapy including biologics has shown improved outcomes in other inflammatory arthritides such as rheumatoid arthritis (RA)[16] but has never been tested in PsA. Given similar efficacy and lower costs seen with TNF inhibitor biosimilar drugs, it is likely that TNF inhibitors represent the most cost-effective option for a first-line biologic treatment.

Therefore, the aim of the Severe Psoriatic arthritis – Early intervEntion to control Disease (SPEED) trial is to establish whether initial intensive therapy with either combination csDMARDs or early biologics affects disease activity at follow-up compared to a step-up treatment approach in moderate/severe PsA. Patients recruited will be required to have one of the recognized poor prognostic markers; thus, they will have to have polyarticular disease ($\geq$5 active joints) or have oligoarthritis ($<$5 active joints) but with other poor prognostic factors [raised C-reactive protein, poor function (health assessment questionnaire, HAQ $>$ 1), radiographic evidence of erosions].

This is a three-arm open-label RCT within a TWiCs cohort (MONITOR-PsA[17]). Participants are randomized 1:1:1 to receive standard therapy in the cohort, initial combination csDMARD therapy or initial TNF inhibitor therapy.

Objectives

Our primary objective is to compare the initial effectiveness of early combination csDMARD therapy (arm 2) and early use of TNF inhibitors (arm 3) with standard step-up care (received in the TWiCs cohort, arm 1) using the PASDAS score[10] (on a continuous scale) at 24 weeks.

Our 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. The cost-effectiveness of the different treatment arms will also be compared with prospectively collected health economics data.

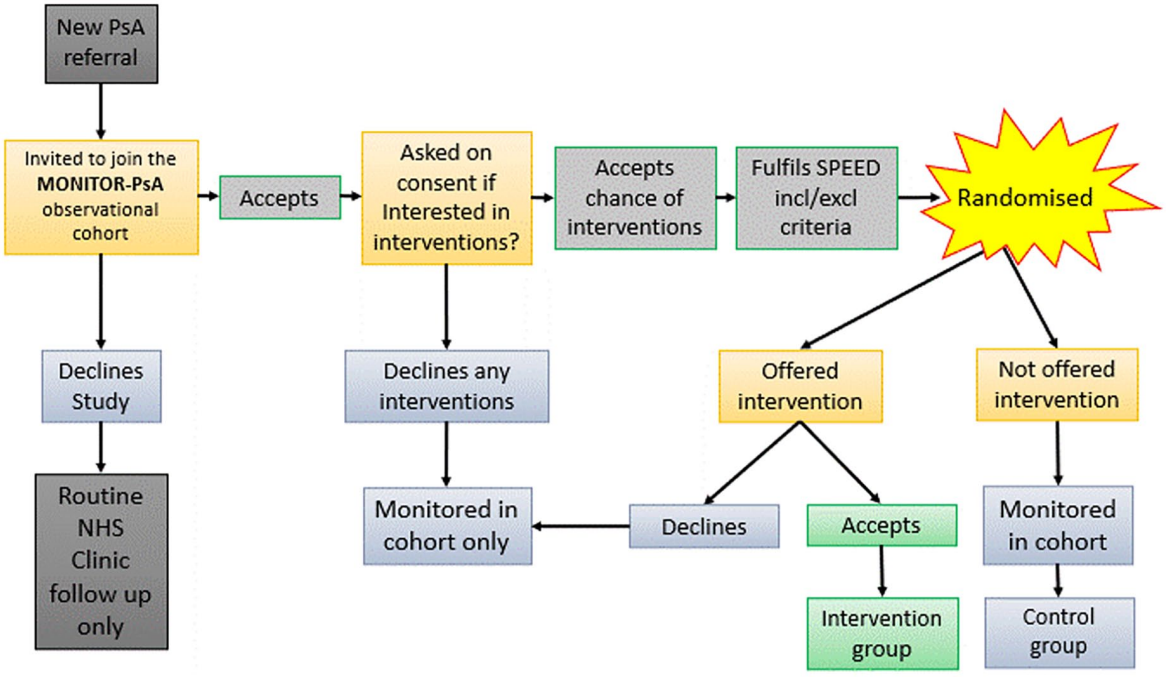

Figure 1. TWiCs design outline.
TWiC, trials within cohort.

Our exploratory objectives include domain-specific responses (e.g. reduction in skin psoriasis, enthesitis, dactylitis), quality of life, treatment satisfaction, safety and radiographic change.

Methods and analysis

The reporting of this study conforms to the Standard Protocol Items: Recommendations for Interventional Trials statement.[18]

Study design

The SPEED study is an open-label RCT of adults with moderate–severe PsA nested within a cohort using a trial within cohorts or TWiCs design. The trial recruits at 11 sites across the UK within the MONITOR-PsA cohort. Participants in the MONITOR-PsA cohort[17] may be offered interventional trials with other members of the cohort acting as comparative controls where they have consented to this. In the SPEED trial, participants in the cohort with moderate–severe diseases are randomized 1:1:1 to standard step-up care, combination csDMARDs or early biologics, with a primary outcome being the PASDAS score after 24 weeks of therapy (see Figure 1). The current protocol is v11 dated 2 March 2023.

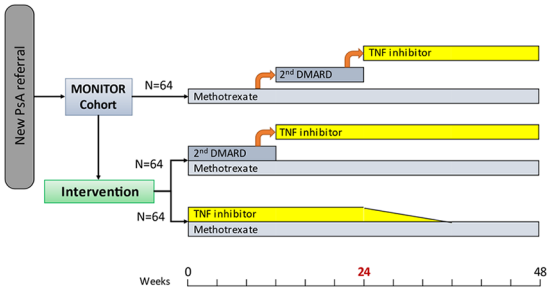

Figure 2. Study design for the SPEED study comparing arm 1 (standard step-up care), arm 2 (combination DMARD) and arm 3 (early TNF inhibitor therapy tapering to stop after 24 weeks).
DMARD, disease-modifying anti-rheumatic drugs; SPEED, Severe Psoriatic arthritis – Early intervEntion to control Disease; TNF, tumour necrosis factor.

Selection of population

This trial recruits participants from the MONITOR-PsA cohort which includes participants with newly diagnosed PsA who have not previously received treatment with any DMARDs for their articular disease. For this trial, only participants with moderate/severe disease defined as those with poor prognostic baseline factors will be eligible (see Table 1).

Table 1. Inclusion and exclusion criteria for the MONITOR-PsA cohort and nested SPEED trial.

MONITOR-PsA cohort	
Inclusion criteria	**Exclusion criteria**
Adults aged 18 or above with a clinical diagnosis of PsA based on the CASPAR criteria (23)	Current or previous treatment of arthritis with synthetic DMARDs (including methotrexate, leflunomide or sulfasalazine) or biologic DMARDs (including TNF, IL12/23 or IL17 inhibitor therapies) or targeted synthetic DMARDs (phosphodiesterase-4 (PDE4) or janus kinase (JAK) inhibitor therapies).
Active PsA is defined by ⩾1 tender or ⩾1 swollen joint or ⩾1 enthesis (site of attachment of tendon to bone)	Use of investigational therapies within 1 month or 5 biological half-lives of the baseline study visit (whichever is longer)
SPEED trial	
Inclusion criteria	Exclusion criteria
Participants have consented to the MONITOR-PsA cohort and to be approached for alternate interventional therapies.	Scheduled elective surgery or other procedures requiring general anaesthesia during the trial.
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)	Patients with a life expectancy of less than 6 months.
Female participants of childbearing potential and male participants whose partner is of childbearing potential must be willing to ensure that they or their partner use effective contraception	Female patient who is pregnant, breastfeeding or planning pregnancy during the trial.
Participant has clinically acceptable laboratory results • Haemoglobin count >8.5 g/dL • White blood cell count (WBC) >3.5 × 109/L • Absolute neutophil count (ANC) >1.5 × 109/L • Platelet count >100 × 109/L • Aspartate transaminase (AST) or alanine transaminase (ALT) and alkaline phosphatase levels <3 × upper limit of normal	Safety issues preventing safe prescription of csDMARDs • Significant renal (estimated glomerular filtration rate <30 mL/min) or hepatic impairment. • Patients who test positive for Hepatitis B, C or HIV. • Contraindication to any of the investigative drugs. • Patients who currently abuse drugs or alcohol
	Any other significant disease or disorder which, in the opinion of the investigator, may put patients at risk because of participation in the trial or may influence the result of the trial or their ability to participate in the trial.
	Participation in another research trial involving an investigational product in the past 12 weeks.
	Additional exclusion criteria apply to patients randomized to arm 3 and receiving adalimumab therapy: • Active TB, chronic viral infections, recent serious bacterial infections, those receiving live vaccinations within 3 months of the anticipated first dose of study medication or those with chronic illnesses that would, in the opinion of the investigator, put the participant at risk. • Latent TB unless they have received appropriate anti-tuberculous treatment as per local guidelines. • History of cancer in the last 5 years, other than non-melanoma skin cell cancers cured by local resection or carcinoma *in situ*.

ANC, absolute neutrophil count; CASPAR, ClasSification of Psoriatic Arthritis; DMARD, disease-modifying anti-rheumatic drugs; IL, interleukins; TB, tuberculosis; TNF, tumour necrosis factor; WBC, white blood count.

Interventions, patient follow-up, visits and trial procedures

During the consent process for the MONITOR-PsA cohort, patients are asked to consent to the following items as part of the TWiCs design.

1. To be contacted by the research team about future interventional studies.
2. To be randomized by the research team for an invitation to participate in these future interventional studies.
3. For anonymized data to be used as a comparison as a control group for these future interventional studies.

If participants consent to the cohort and consent to be contacted about future interventional studies, then their baseline data will be reviewed to see if they fulfil the inclusion/exclusion criteria for the SPEED study. If they are potentially eligible, they undergo an initial randomization using an automated, secure, 24-h internet randomization service, either to remain in the cohort as a control subject or to be offered one of the two interventions (Figure 2).

Participants are randomized by the local research team in a 1:1:1 allocation ratio to the three treatment arms using a minimization algorithm[19–21] with a probabilistic element of 0.8, stratified by centre, arthritis subtype (polyarticular *versus* oligoarticular) and symptom duration (<12 months, $\geqslant 12$ months). If they are randomized to the offer of an additional intervention, rather than to standard care, a specific trial patient information sheet is provided and additional consent for the trial is sought by a clinician (see Supplemental Material 1 consent forms). As SPEED is an interventional trial, consent must be taken by a physician. The randomization process is a two-stage procedure. The second stage confirms consent and eligibility for the particular treatment arm allocated. For participants allocated to arms 2 and 3, the second stage is to be completed once consent for the intervention and any additional required screening assessment have been completed.

The trial lasts 48 weeks with study visits every 12 weeks from week 0 to week 48 within the MONITOR-PsA cohort,[17] in line with clinical practice for recently diagnosed inflammatory arthritis patients. There is no blinding of therapy allocation for patients or clinicians, so no allocation code or code-breaking procedure is required. At the study visits, assessments include patient-reported outcomes (questionnaires), clinical assessment of disease activity, laboratory measures of inflammation and assessment of safety on therapy. As therapy within the trial is unblinded, clinical assessments at the study visits are performed by an appropriately trained blinded assessor to reduce bias.

The interventions involve four investigational medicinal products: methotrexate, sulfasalazine, leflunomide and adalimumab. Participants are randomized to an initial treatment combination using these medications, but if participants cannot tolerate the medications or if they are not effective, then they are switched to rescue therapy. Patients randomized to arm 1 receive standard 'step-up' therapy in line with the cohort (MONITOR-PsA study) as the control group. While physician discretion is used, the most common initial therapy is methotrexate alone (15 mg/week rising to 25 mg/week as tolerated by week 8 of therapy) unless this is contraindicated. In cases of non-response or intolerance to methotrexate, participants are prescribed an alternative csDMARD (most commonly sulfasalazine or leflunomide) added or switched to at the discretion of the rheumatologist. In cases of failure of two csDMARDs and ongoing active disease, treatment can be escalated to biologic therapy if National Institute for Health and Clinical Excellence (NICE) recommendations[22–25] are met, usually with a TNF inhibitor as the first line.

Arm 2 is the combination DMARD arm. All participants have been prescribed methotrexate with an additional csDMARD (either sulfasalazine increasing to 2 g, potentially up to 3 g daily or leflunomide 10–20 mg daily) at baseline, staggering the start of these therapies by 1 week to allow more accurate attribution of adverse events. Either sulfasalazine or leflumonide is chosen depending on physician preference (considering disease presentation, arthritis, enthesitis, skin disease, risk of hypertension and liver disease). Similar to arm 1, in cases of failure of two csDMARDs and ongoing active disease, treatment can be escalated to biologic therapy if NICE recommendations[22–25] are met, usually with a TNF inhibitor as the first line. This would be classified as rescue therapy.

Arm 3 is the early biologic arm. All participants are prescribed methotrexate (given weekly) with a

TNF inhibitor (adalimumab 40 mg given every 2 weeks) at baseline staggering the start of these therapies by 1 week to allow more accurate attribution of adverse events. Treatment with TNF inhibitor is continued until week 24 at which time the TNF inhibitor is tapered by extending the dose interval to week 28 and week 32. The TNF inhibitor is stopped completely after week 32 and participants continue methotrexate as standard care. At the end of the study, patients will be able to continue on their current medication as part of standard clinical care. In all arms, oral and subcutaneous methotrexate are permitted with the choice left to the treating clinician and patient.

The response is assessed in all groups after 12 weeks of therapy using the MDA criteria.[26] Participants who achieve the MDA criteria by week 12 will continue on their current therapy. Participants who have a reduction in tender and swollen joint counts of at least 20% by week 12 but do not yet meet the MDA criteria continue their therapy for an additional 12 weeks. Participants failing to tolerate the medications prescribed (participant intolerance, adverse events necessitating treatment change or investigator's opinion) or show a reduction in joint counts by less than 20% by week 12 or those failing to meet MDA criteria by week 24 are eligible to receive rescue therapy. This may be in addition to the prescribed trial medication or as an alternative treatment. Participants may be eligible at this time point for biologic therapy under NICE guidelines. All medication use related to PsA will be recorded for analysis but as the study is pragmatic, drug adherence is only assessed by patient report.

Sample size

The primary outcome is the PASDAS score[10] (on a continuous scale) at 24 weeks. The primary null hypothesis is a global assessment of no difference between any of the means of the PASDAS score of the three treatment arms.

This study was originally powered for a PASDAS good response[27] binary outcome using data from TIght COntrol of PsA (TICOPA) study to inform the likely response of the step-up cohort control arm. A PASDAS good response is defined as a reduction from baseline of at least 1.6, with a final score of $\leqslant 3.2$. Assuming 30% of participants in the control arm achieve this response 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%, that is, that 50% achieve a PASDAS good response in the active arms by 6 months.

A change to the way the primary outcome is specified was approved by the Trial Steering Committee and implemented in 2022 to use the PASDAS score on a continuous scale rather than as a binary outcome. Based on the following assumptions: 80% power and 5% two-sided statistical significance to detect a minimally clinically important difference (MCID) of 0.8 on the PASDAS score as a 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.*[28] The standard deviation is based on the observed variability in the continuous PASDAS score in the MONITOR cohort.[17]

Recruitment

At each participating site, enrolment will occur at rheumatology outpatient clinics. The study was initially planned to have 3 sites but has been expanded to a total of 11 sites across the UK. The trial opened for recruitment at the first site in April 2018 and the estimated recruitment completion date is January 2024.

Outcomes

In the original conception of the study, the primary study endpoint was the proportion of participants achieving a PASDAS good response at week 24 between any of the three treatment arms. As stated above, the primary endpoint was changed from this binary outcome to the PASDAS score at 24 weeks on a continuous scale. The PASDAS is a composite score including both clinical assessment and patient-reported outcomes. It is calculated as $[((0.18\sqrt{}\text{physcian global VAS}) + (0.159\sqrt{}\text{patient global VAS}) - (0.253 \times \sqrt{}\text{SF36-PCS}) + (0.101 \times \text{LN (SJC} + 1)) + (0.048 \times \text{LN (TJC} + 1)) + (0.23 \times \text{LN (Leeds enthesitis index} + 1)) + (0.37 \text{ LN (tender dactylitis count} + 1)) + (0.102 \times \text{LN (CRP} + 1)) + 2)] \times 1.5$, where LN is natural logarithm, PCS is the physical component summary scale of SF36, CRP is the C-reactive protein in mg/L and

Table 2. Secondary outcome measures for the SPEED trial.

Domain	Validated instrument to be used	Endpoints
Composite measures	PASDAS[10] (calculated using all outcomes) MDA[26]	PASDAS score, good response[27] (reduction of ⩾1.6 and final score of ⩽3.2) and PASDAS moderate response[27] (reduction of ⩾1.6 or final score of ⩽3.2) The proportion achieving MDA 5/7 and 7/7
Musculoskeletal disease activity	Physician global VAS, 68 TJC and 66 SJC[31] Leeds[32] and SPARCC[33] enthesitis index, dactylitis count[34]	Within PASDAS/MDA Median change in enthesitis/dactylitis count Proportion with resolution of enthesitis/dactylitis
Skin disease activity	PASI[35]	PASI 75 and PASI 90
Systemic inflammation	C-reactive protein	Within PASDAS
Patient global	Global disease activity VAS[36]	Within PASDAS
Pain	Patient pain VAS[31]	Within MDA
Physical function	HAQ[37]	Proportion achieving MCID (0.35)
Overall impact	PSAID[38]	Proportion achieving relevant absolute change (⩾3) Proportion achieving patient acceptable symptom state (⩽4)
Fatigue	PSAID	As before
Health-related quality of life	SF36[39] EQ-5D-5L[40] PSAID[38]	Within PASDAS For health economics analysis As before
Participation	WPAI[41] PSAID[38]	Absenteeism, presenteeism, productivity loss As before
Emotional wellbeing	PSAID[38]	As before
Structural damage	Sharp–van der Heijde radiographic score[42] (48 weeks only)	Cumulative probability plots

HAQ, health assessment questionnaire; MCID, minimally clinically important difference; MDA, minimal disease activity; PASDAS, PsA disease activity score; PASI, psoriasis area and severity index; 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.

SF36 is the Medical Outcomes Study Short Form-36. All visual analogue scale (VAS) scores are 0–100 mm. The joint count used is the 68 (tender) and 66 (swollen) joint count. The PASDAS score range is 0–10, with higher values indicating worse disease activity. The PASDAS score was chosen as a validated PsA-specific measure that encompasses multiple domains of PsA.[29]

Individual secondary outcome measures covering all of the new 2016 Outcome Measures in Rheumatology Clinical Trials core and strongly recommended domains for PsA studies[30] are collected at all timepoints. The secondary outcome measures are listed in Table 2. In addition to this, key adverse events likely to be related to the investigational drugs are also collected at each study visit. The electronic case report form system

OpenClinica is used to collect the data at most sites, with data at the Cambridge site collected *via* a local Epic database and transferred to the study team. A data management plan is in place to outline all data arrangements.

Statistical analysis plan

The trial analysis will take place after all participants have completed their follow-up. No interim analyses are planned. Full details of the statistical analysis will be provided in a separate statistical analysis plan which will be finalized prior to the primary analysis data lock. STATA (StataCorp LP, College Station, Texas, USA) or other validated statistical software will be used for the analysis.

The analysis population will be the intention-to-treat population and therefore participants will be analysed based on their randomization assignments.

Missing data assumptions made for the analyses will be clearly stated and multiple imputations will be considered for data missing at random. A sensitivity analysis will be carried out to investigate the robustness of findings, to compare the plausibility of the missing data assumptions and to compare the results with a complete case analysis.

A hierarchical method of testing will be used to compare the three treatment groups. 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. If this null hypothesis is rejected at the 5% level, each intervention will be compared against the control 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 csDMARD 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). 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 and the treatment difference will be reported with a 95% confidence interval.

Table 3. PASDAS response criteria.

	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

PASDAS, PsA disease activity score.

The association between the primary outcome, PASDAS score at 24 weeks and the treatment groups will be analysed using linear regression. The linear model will be adjusted for stratification factors (centre, arthritis subtype and symptom duration) and the baseline PASDAS score. The estimates of the mean difference between each treatment group and the control groups will be presented with the corresponding 95% confidence interval.

Complier average causal effect analysis[43] will also be undertaken to take into account adherence to the randomized treatments for the primary outcome analysis.

Key secondary outcomes will include the following :

- Time from baseline to MDA response where MDA is defined as meeting five of the following seven criteria: TJC ⩽1; SJC ⩽1; psoriasis activity and severity index ⩽1; patient pain VAS ⩽15 mm; patient global VAS ⩽20 mm; HAQ ⩽0.5; tender entheseal 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.

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. A hierarchical method of testing, as described for the primary outcome measure, will be used for continuous secondary outcomes and estimates, 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 csDMARD 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.

The health economic evaluation will estimate the cost-effectiveness of the three arms using direct and indirect costs collected prospectively in the trial by physician and patient report. Health-related quality of life will be estimated using the EuroQol (EQ-5D-5L). Unit cost data will be obtained from national databases such as the BNF and PSSRU Costs of Health and Social Care. A within-trial evaluation will be conducted from a UK NHS and Personal Social Services perspective and outputs of the cost-effectiveness analysis will be presented in terms of expected incremental cost-effectiveness ratios.

Monitoring

The study is managed by a trial management committee including the chief investigator (CI), laboratory lead and Oxford Clinical Trials Research Unit (OCTRU) staff. An independent trial steering committee and data safety and monitoring committee consisting of rheumatologists, statisticians and patient partners oversee the MONITOR-PsA and SPEED studies. 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 the green light in line with OCTRU standard operating procedures (SOPs). These audits are independent from the investigators but not independent from the Sponsor.

Patient and public involvement (PPI)

The lack of data informing treatment selection is frustrating for clinicians and 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 PsA including non-drug and drug treatments?' was ranked highest in the top 10 unmet needs. Patient research partners from the British PsA Consortium assisted with the design of the study including the research question, the timing of follow-up visits and selection of outcome measures. Two patient partners living with PsA sit on the trial steering committee overseeing the MONITOR-PsA cohort and the SPEED trial throughout and will help with the dissemination of the future results.

Ethics and dissemination

The SPEED trial is being conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Approval from the Health Research Authority and the South-Central Research Ethics Committee with reference 18/SC/0107. All significant changes to the protocol have been reviewed by the ethics committee and, if appropriate, by the Medicines Health Regulatory Authority (MHRA). Collection of personal data is minimized within the study, with identifiable data being held securely to maintain confidentiality before, during and after the trial.

The deliverables from this project will include peer-reviewed publications describing the initial 24-week trial outcome and subsequent outcomes at week 48 and beyond in the MONITOR cohort. Alongside data from other similar studies such as the COMPLETE-PsA study,[44] we hope that the SPEED study will influence national and international treatment recommendations for PsA. Health economic data from our study will help to estimate the cost-effectiveness of combination therapies.

Protocol amendments

The SPEED study currently uses V11 of the protocol. Version 3 was the first approved protocol in use following amendments for initial REC and MHRA review. Significant changes after that include the following:

- V4 – change to sample handling process and inclusion of British Society for

Rheumatology recommendations for DMARD prescription.
- V5 – Addition of new study sites, reduction of Bath ankylosing spondylitis metrology index (BASMI) measurement frequency to annual.
- V6 – clarification of labelling required for trial-specific IMP.
- V7 – clarification of inclusion criteria, allowance of remote assessment for a 36-week visit.
- V8 – Extension of trial dates.
- V9 – Addition of new study sites, an extension of trial dates, Regulation 46 (2) of SI 2004/1031 applied to labelling of non-trial specific investigational medicinal products (IMPs).
- V10 – Change to primary outcome from binary to continuous scale and updated sample size, extension of trial dates, ultrasound scan removed.
- V11 – Extension of trial dates, addition of new funders.

Declarations

Ethics approval and consent to participate

Ethical approval for the study was granted by the South Central Research Ethics Committee (ref 18/SC/0107). All participants in the study gave written, informed consent for participation in the MONITOR-PsA cohort and in the SPEED study.

Consent for publication

Not applicable.

Author contributions

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Competing interests

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. WRT has received grants/research support from Abbvie, Celgene, Eli Lilly, Janssen, Pfizer and UCB, and as a paid consultant for AbbVie, Amgen, Bristol Myers Squibb, Celgene, Eli Lilly, GSK, Janssen, Novartis, Ono-Pharma, Pfizer and UCB and as a paid speaker from AbbVie, Amgen, Bristol Myers Squibb, Celgene, Eli Lilly, GSK, Janssen, Novartis, Ono-Pharma, Pfizer and UCB. DRJ has received grants for research or education from AbbVie, Amgen, Biogen, Boehringer Ingelheim, Celgene, Eli Lilly, Fresenius Kabi,

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Availability of data and materials

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 to maintain participant anonymity.

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Supplemental material

Supplemental material for this article is available online.

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