Trial Title: 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.

Short title: Severe Psoriatic arthritis – Early intervEntion to control Disease: the SPEED trial

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Chief Investigator Signature: 

Statistician Signature: ……

Potential conflicts of interest: Laura Coates – received honoraria from Abbvie

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, Health Research Authority (HRA), host organisation, and members of the Research Ethics Committee (REC), unless authorised to do so.

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1. KEY TRIAL CONTACTS

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2. SYNOPSIS

Trial Title	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.	
Short title	Severe Psoriatic arthritis – Early intervEntion to control Disease: the SPEED trial	
Clinical Phase	Phase IV	
Trial Design	Randomised controlled trial within Trials Within Cohorts (TWiCs) design	
Trial Participants	Patients from the MONITOR-PsA cohort with moderate/severe psoriatic arthritis	
Planned Sample Size	192, 64 per trial arm.	
Sites	5-15 sites	
Treatment duration	36-48 weeks	
Follow up duration	36-48 weeks.	
Planned Trial Period	15 April 2018 to Oct 2024	
	Objectives	**Outcome Measures**
Primary	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.	PsA Disease Activity Score (PASDAS)[1] (on a continuous scale) at 24 weeks in each of the three treatment groups (standard step up therapy in the cohort, early combination DMARD or early TNF inhibitor therapy) at 24 weeks post randomisation.
Secondary	To assess the speed of response to therapy in the treatment arms	Time to achievement of minimal disease activity (MDA) (as detailed in section 4.1 and 11.1)
	To assess overall effectiveness of the treatment arms	PASDAS moderate response (as detailed in section 11.1) at 24 and 48 weeks post randomisation PASDAS score (on a continuous scale) at 48 weeks post randomisation.
	To assess later effectiveness of the treatment arms	The proportion of patients achieving a PASDAS good response (as detailed in section 11.1) at 24 weeks and 48 weeks post randomisation
	To assess the effectiveness of the treatment arms on patient life impact	Proportion of patients meeting reduction of at least 3 points on the PsA impact of

		disease (PsAID) score at 24 and 48 weeks post randomisation
	To assess the cost-effectiveness of the treatment arms	Cost per QALY in each treatment arm to calculate ICER. See section 11.2 below
Exploratory objectives	To evaluate exploratory outcome measures that may be used to generate hypotheses for future studies. They may be required in later studies on the cohort as part of the TWiCs approach. ACR20, 50 and 70[23]	• Disease Activity in PsA (DAPSA) response rates[24] at week 24, 48. • Percentage change and proportion with resolution in enthesitis score • Percentage change and proportion with resolution in dactylitis count • PASI75 and PASI90[25] • Change in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[26] and Bath ankylosing spondylitis metrology index (BASMI)[27] for those with axial disease • PASDAS response and proportion with inactive disease for those with axial disease. • Treatment satisfaction measured by the treatment satisfaction questionnaire for medication (TSQM)[28] • Change in modified Sharp-van der Heijde radiographic score for PsA [29] and PsA Ratingen Score (PARS) [30] at week 48. • Safety (AEs, ADRs and SAEs reported during the trial period)
Investigational Medicinal Products	Methotrexate Sulfasalazine Leflunomide Adalimumab	
Formulation, Dose, Route of Administration	Methotrexate tablets, 5-25mg weekly, oral or subcutaneous injection Sulfasalazine, 0.5-3g daily, oral administration Leflunomide 10-20mg daily, oral administration Adalimumab 40mg every 2 weeks, subcutaneous injection See section 4 below for additional detail	

3. ABBREVIATIONS

ACPA	Anti Citrullinated Peptide Antibody
ACR	American College of Rheumatology
AE	Adverse event
AR	Adverse reaction
BASDAI	Bath ankylosing spondylitis disease activity index
BASMI	Bath ankylosing spondylitis metrology index
BSA	Body surface area
CI	Chief Investigator
CRF/eCRF	Case Report Form/electronic Case Report Form
CRP	C-reactive protein
CTRG	Clinical Trials and Research Governance
DMARD / csDMARD / bDMARD	Disease-modifying anti-rheumatic drug / conventional synthetic disease-modifying anti-rheumatic drug / biologic disease-modifying anti-rheumatic drugs
DSMC	Data Safety and Monitoring Committee
DSUR	Development Safety Update Report
EMS	Early morning stiffness
EULAR	EUropean League Against Rheumatism
EuroQol	European Quality of Life
FBC	full blood count
GCP	Good Clinical Practice
GP	General Practitioner
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HRA	Health Research Authority
IBP	Inflammatory back pain
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
LEI	Leeds enthesitis index
LFTs	Liver function tests
MDA	Minimal disease activity
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
OCTRU	Oxford Clinical Trials Research Unit
PARS	PsA Ratingen Score
PASDAS	Psoriatic arthritis disease activity score

PASI	Psoriasis area and severity index
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
PROM	Patient reported outcome measures
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
RRAMP	Registration / Randomisation and Management of Product
R&D	NHS Trust R&D Department
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RF	Rheumatoid factor
RNHRD	Royal National Hospital for Rheumatic Diseases
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SF36	Short Form (36) Health Survey
SJC	Swollen joint count
SmPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SPARCC	Spondyloarthritis Research Consortium of Canada
SUSAR	Suspected Unexpected Serious Adverse Reaction
TJC	Tender joint count
TMF	Trial Master File
TMG	Trial Management Group
TNF	Tumour necrosis factor
TSC	Trial Steering Committee
TSQM	Treatment satisfaction questionnaire for medication
TWiCs	Trials Within Cohorts
U&Es	Urea and electrolytes
US	Ultrasound
VAS	Visual Analogue Scale
WPAI	Work productivity and activity impairment

4. BACKGROUND AND RATIONALE

Psoriatic arthritis (PsA) is an inflammatory arthritis estimated to occur in 15% of people with psoriasis[3] affecting around 150,000 people in the UK[4]. Audit data from Oxford in 2015 shows that 21.5% of patients in the early arthritis clinic have a diagnosis of PsA. Two thirds of people with PsA suffer progressive joint damage with associated increasing disability [5, 6]. After equal disease duration, people with PsA and rheumatoid arthritis (RA) have similar functional and quality of life impairment[7]. PsA is associated with a reduced life expectancy[8] partially related to the significant risk of comorbidities, particularly the metabolic syndrome[9]. Direct costs to healthcare are estimated at £2,400 per patient annually with indirect costs (time lost from work and activities) per patient of over £8,000[10].

Both recent International treatment recommendations published by the EUropean League Against Rheumatism (EULAR) and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) utilise a "step up" approach to treatment[11, 12]. 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[13] but there are no studies that have previously used them to guide therapy.

Combinations of disease-modifying anti-rheumatic drugs (DMARDs), usually methotrexate with a second DMARD, have been shown to have some advantages over single therapies in PsA[14] but there are no large well-designed studies reporting on this and none using combination DMARD at diagnosis. These drugs are affordable in most healthcare systems and very frequently prescribed in PsA but do have problems with patient tolerability and can cause significant side effects[15].

Early use of tumour necrosis factor (TNF) inhibitors has also been shown to be superior to methotrexate in a head to head open label trial[16] but there is no data on long term outcomes. Randomised Controlled Trials (RCTs) of TNF inhibitors in PsA have shown that the improvement in those initially receiving 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[17]. 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 course of "early biologics", where patients receive a course of TNF inhibitor 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 early biologics has shown improved outcomes in other inflammatory arthritides such as RA [18] but has never been tried in PsA.

Therefore the aim of this study is to establish in a full RCT whether initial intensive therapy with either combination DMARDs 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 (≥5 active joints) or to have oligoarthritis (<5 active joints) but with other poor prognostic factors (raised C reactive protein, poor function, radiographic evidence of erosions).

This is a three arm open label RCT within a TWiCs cohort (Monitor-PsA REC Ref 17/SC/0556). Participants will be randomised 1:1:1 to receive standard therapy in the cohort, be offered initial combination DMARD therapy or to be offered initial TNF inhibitor therapy.

Following a review of the sample size following slower than expected recruitment, and in agreement with the DSMC and TSC committees, a change to the way the primary outcome is specified has been implemented.

To enable the trial to complete as planned with sufficient power and to answer the original research question, this 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. Specifying in this way reduces the sample size and has been enabled by the development of the minimally clinically important difference for this outcome measured on the continuous scale. Also, during the initial design of the trial there was limited data available on PASDAS, however the COMPLETE-PsA trial has provided additional information and evidence on using PASDAS as an outcome.

4.1. Proposed interventions

A schema of the proposed interventions is shown in Appendix A.

ARM 1: Control 'step-up' therapy in the cohort (MONITOR-PsA study). Therapy for the cohort is defined by standard NHS practice in these PsA clinics following current international recommendations[11] and National requirements for the prescription of biologic therapy[19-22]. Whilst physician discretion is used, most commonly Initial therapy will be with methotrexate alone (15mg/week rising to 25mg/week as tolerated by week 8 of therapy) unless this is contraindicated. In cases of non-response or intolerance to methotrexate, participants will have an alternative DMARD (most commonly sulfasalazine or leflunomide) added or switched to at the discretion of the rheumatologist. In cases of failure of two DMARDs, treatment can be escalated to biologic therapy as per National Institute for Health and Clinical Excellence (NICE) recommendations[19-22] usually with a TNF inhibitor as first line. If the requisite disease activity is not met or if there are contraindications to biologics, alternative DMARD combinations will be used. Further details are available in the PsA clinic treatment protocol which is Appendix D in the MONITOR-PsA protocol.

ARM 2: Combination DMARD arm. All participants will be prescribed methotrexate with an additional DMARD (either sulfasalazine or leflunomide) at baseline, staggering the start of these additional therapies by one week to allow more accurate attribution of adverse events. Either sulfasalazine or leflumonide will be used in combination depending on physician preference (taking into account disease presentation, arthritis, enthesitis, skin disease, risk of hypertension and liver disease). Response will be assessed after 12 weeks of therapy using the Minimal Disease Activity (MDA) criteria. These assess 7 different outcomes and patients should meet at least 5 of the 7 items to be classified as being in MDA. The MDA criteria are shown in the box below:

Outcome Measure (see Section 8)	**Score +1 for each outcome measure which is below the value below.** **Total score of ≥5 indicates MDA achieved**
Tender joint count (TJC) (using 68 joint count)	≤1
Swollen joint count (SJC) (using 66 joint count)	≤1
Enthesitis count (using LEI or SPARCC)	≤1
Skin assessment	PASI≤1 or BSA≤3%
Patient global VAS (mm)	≤20
Patient pain VAS (mm)	≤15
HAQ	≤0.5

Participants who achieve the MDA criteria by week 12 on this combination therapy will continue on this therapy. Participants who show a significant response by week 12 (a reduction in tender and swollen joint counts of at least 20%) but do not yet meet the MDA criteria should continue on this therapy for an additional 12 weeks before review. Participants failing to tolerate the medications prescribed (participant intolerance, adverse events necessitating treatment change or investigators opinion) or show significant response (reduction in joint counts by less than 20%) by week 12 on this combination therapy or those failing to meet MDA criteria by week 24 will be eligible to receive rescue therapy following the standard PsA clinic treatment protocol (as per arm 1 above and as detailed in the PsA clinic treatment protocol which is found in appendix D of the MONITOR-PsA protocol). 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 most commonly using TNF inhibitors under NICE guidelines. These state that patients should have failed adequate trials of at least 2 standard DMARDs and that they should have active disease defined as at least 3 tender and 3 swollen joints. If they do not fulfil these NICE criteria (≥3 tender and ≥3 swollen joints) they will be prescribed alternative DMARDs.

ARM 3: Early biologic arm. All participants will be prescribed methotrexate (given weekly) with a TNF inhibitor (adalimumab given every two weeks) at baseline staggering the start of these therapies by one week to allow more accurate attribution of adverse events (TNF inhibitor from week 0, methotrexate from week 1). Treatment with TNF inhibitor will be continued until week 24 at which time the TNF inhibitor will be tapered by spacing out doses which will be received at week 28 and week 32. The TNF inhibitor will be stopped completely after week 32 and participants will continue on methotrexate as standard care. In case of intolerance to either of the medications or a flare of disease, participants will be eligible for rescue therapy following the standard PsA clinic treatment protocol (as per arm 1 above and as detailed in the PsA clinic treatment protocol which is found in appendix D of the MONITOR-PsA protocol). According to this protocol they will be switched to an alternative DMARD (if methotrexate is not tolerated by the patient due to side effects) or started on combination DMARD therapy (sulfasalazine or leflunomide alongside methotrexate) and may subsequently be eligible for further TNF inhibitor treatment at a later point if they fulfil NICE criteria (as above). All medication use related to PsA will be recorded for analysis. This may be in addition to the prescribed trial medication or as an alternative treatment.

The Investigational Medicinal Products (IMPs) used in this trial are methotrexate, sulfasalazine, leflunomide and adalimumab. All of these medications are used routinely in PsA patients in standard care. Methotrexate and sulfasalazine are not licensed for PsA but are both licensed for rheumatoid arthritis and methotrexate is also licensed for use in psoriasis. Further summary details are included about the drugs below:

4.2. Methotrexate (DMARD)

Methotrexate is a conventional synthetic disease-modifying anti-rheumatic drugs (csDMARD) and the most commonly prescribed first line therapy in PsA. It is an immune suppressant licensed for the treatment of psoriasis and rheumatoid arthritis, although it does not have a licence for treatment of PsA. Common side effects include nausea, fatigue, mouth ulcers, raised liver enzymes and leucopenia. It is given orally or subcutaneously in doses from 5-25mg given once per week in line with local treatment protocol or local policy taking into account patient preference, GI side effect risk, severity of disease and medications already being taken. Methotrexate will be prescribed for both interventional trial arms as the first line therapy either concomitantly with another DMARD (in arm 2) or adalimumab (in arm 3). It will usually be prescribed at 15mg per week for the first 4 weeks, 20mg per week for the next 4 weeks and 25mg per week thereafter as tolerated and based on clinician opinion. However if not tolerated, lower doses will be used within the range 5-20mg.

4.3. Sulfasalazine (DMARD)

Sulfasalazine is a csDMARD and is one of the commonly prescribed second line therapies in PsA. It is an immune suppressant licensed for the treatment of rheumatoid arthritis although it does not have a licence for the treatment of PsA. Common side effects include nausea, fatigue, rash and leucopenia. It is given orally in doses from 0.5-3g daily in two or three divided doses. It is one of the second line DMARDs that may be used in combination with methotrexate in arm 1 of the trial. In arm 2 it will be a first line option. It will be prescribed with a standard increasing dose over the first 4 weeks aiming for an initial dose of 1g orally twice per day with the potential to increase up to 3g/day.

4.4. Leflunomide (DMARD)

Leflunomide is a csDMARD and is one of the commonly prescribed second line therapies in PsA. It is an immune suppressant licensed for the treatment of PsA. Common side effects include nausea, fatigue, diarrhoea and raised liver enzymes. It is given orally in doses from 10-20mg daily. It is one of the second line DMARDs that may be used in combination with methotrexate in arm 1 of the trial. In arm 2 it will be a first line option. It will be prescribed at an initial dose of 10mg per day with the potential to increase to 20mg per day if disease is not controlled. Leflunomide will not be used in patients with ALT>1.5 x upper limit of normal, in any case with baseline liver abnormalities, sulfasalazine will be used as the second DMARD with caution on dose and regular blood monitoring.

4.5. Adalimumab (TNF inhibitor)

Adalimumab is a biologic disease-modifying anti-rheumatic drug (bDMARD) and is one of the commonly prescribed biologic therapies in PsA. It is a humanised monoclonal antibody directed against tumour necrosis factor (TNF) alpha (a TNF inhibitor). It is an immune suppressant licensed for the treatment of psoriatic arthritis in patients who have failed csDMARDs. Common side effects include increased frequency of infections, headache, injection site reaction, skin rash, sinusitis and antibody development. It is given by subcutaneous injection at a dose of 40mg every other week. In arm 3 it will be used a first line therapy.

5. OBJECTIVES AND OUTCOME MEASURES

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
<u>Primary Objective</u> 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)	The primary outcome is the PASDAS score (on a continuous scale). This will be reported as a continuous outcome in each of the three treatment groups (standard step up therapy in the cohort, early combination DMARD or early TNF inhibitor therapy) at week 24.	Clinical assessment, patient questionnaires and blood tests all performed at weeks 0 and 24
<u>Secondary Objectives</u> To assess the speed of response to therapy in the treatment arms		Assessment every 12 weeks

	Time to achievement of minimal disease activity (MDA) (as detailed in section 4.1 and 11.1)	
To assess later effectiveness of the treatment arms	The proportion of patients achieving a PASDAS good response at week 24 and 48 PASDAS score (on a continuous scale) at 48 weeks.	Clinical assessment, patient questionnaires and blood tests all performed at weeks 0, 24 and 48.
To assess overall effectiveness of the treatment arms	PASDAS moderate response (as detailed in section 11.1) at 24 and 48 weeks post randomisation	Clinical assessment, patient questionnaires and blood tests all performed at weeks 0, 24 and 48.
To assess the effectiveness of the treatment arms on patient life impact	Change inPsA impact of disease (PSAID) score from baseline to follow up. Proportion achieving PSAID patient acceptable symptom state (score ≤4) at follow up Change in work productivity (absenteeism, presenteeism and productivity loss) as measured by WPAI at follow up	Patient questionnaires at weeks 0, 24, and 48 weeks
To assess the cost-effectiveness of the treatment arms	Cost per QALY in each treatment arm to calculate ICER	Healthcare resource use data and health related quality of life throughout the study.
<u>Exploratory objectives</u> To evaluate exploratory outcome measures that may be used to generate hypotheses for future studies. They may be required in later studies on the cohort as part of the TWiCs approach.	• ACR20, 50 and 70[23] • Disease Activity in PsA (DAPSA) response rates[24] at week 24, 48. • Percentage change and proportion with resolution in enthesitis score • Percentage change and proportion with resolution in dactylitis count • PASI75 and PASI90[25] • Change in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[26] and Bath ankylosing spondylitis metrology index (BASMI)[27] for those with axial disease	All follow-up visits where measured – as detailed in Appendix C schedule of procedures

	• ASDAS response and proportion with inactive disease for those with axial disease. • Treatment satisfaction measured by the treatment satisfaction questionnaire for medication (TSQM)[28] • Change in modified Sharp-van der Heijde radiographic score for PsA [29] and PsA Ratingen Score (PARS) [30] at week 48. • Safety (AEs, ADRs and SAEs reported during the trial period) •	

6. TRIAL DESIGN

A flowchart of the trial design is shown in appendix A.

This is a randomised 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 192 participants will be recruited (64 to the cohort as controls and 128 receiving the interventions: 64 in arm 2 and 64 in arm 3). Each participant will be followed for a maximum 48 weeks within this trial and will then revert to standard care within the cohort.

Participants in this study will attend for study visits at baseline and weeks 12, 24, 36 and for participants enrolled early in the trial at 48 (see below for further details). At the 12 weekly visits, participants will be assessed clinically for disease activity and will be asked to complete patient reported outcomes via questionnaires. Visits in between these will be performed based on clinical need where adjustment to therapy is required.

Participants will need to attend a face to face clinic appointment every 12 weeks for the assessments to be carried out to determine if the participant meets MDA. If the participant does not meet MDA, treatment will need to be escalated. This cannot be assessed remotely meaning treat to target cannot be implemented unless participants are seen face-to-face. Therefore participants will need to attend clinic at baseline, 12 weeks, 24 weeks, 36 weeks and 48 weeks (if within the study follow up period – see below for further details). However, if the participants are stable, their disease is under control and they have previously met target MDA, and they are unable to be reviewed within the hospital the 36 week assessment could be carried out remotely.

Not all patients will complete the week 48 follow up assessments. Those patients recruited within the last 24 weeks of recruitment, will only have visit assessments conducted up to week 36. Investigational medicinal product (IMP) will be provided for these patients until week 32. A week 36 assessment will be completed which includes a safety assessment. All Adalimumab will be supplied as study stock until week 32 as previously outlined. Conventional DMARDs (methotrexate, leflunomide, sulfasalazine) will be provided as

study medication until week 32. Participants will then continue their medication via standard NHS prescriptions.

Participants in arm 2 and 3, will be able to attend for rescue therapy as required via the rheumatology helpline as in standard care. After a SPEED participant has had their week 48 visit or for those recruited in the last 24 weeks of recruitment, after their week 36 visit, they will revert to the follow up visits as outlined in the MONITOR cohort. Their treatment (medication) will be standard care and clinical assessment data will be collected through the MONITOR cohort with appropriate patient consent.

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. These assessments are detailed in section 8.

7. PARTICIPANT IDENTIFICATION

7.1. Trial Participants

This trial will recruit participants from MONITOR-PsA with newly diagnosed PsA who have not previously received treatment with 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 below).

7.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the trial.
- Male or Female, aged 18 years or above.
- Participants consented to the PsA inception cohort (MONITOR-PsA) and to be approached for alternate interventional therapies.
- Poor prognostic factors at baseline. Either
    - Polyarticular disease with ≥5 active joints at baseline assessment OR
    - Oligoarticular disease with <5 active joints at baseline but with one or more of the following poor prognostic factors: raised C reactive protein, radiographic damage, health assessment questionnaire>1
- Female participants of child bearing potential and male participants whose partner is of child bearing potential must be willing to ensure that they or their partner use effective contraception[1] during the trial and for 3 months thereafter (or 2 years if received leflunomide unless treated with washout therapy) as in standard practice.
- Participant has clinically acceptable laboratory results within 12 weeks of SPEED baseline (i.e. the second registration in RRAMP being completed).
    - 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
- In the Investigator's opinion, is able and willing to comply with all trial requirements.
- Willing to allow his or her GP and consultant, if appropriate, to be notified of participation in the trial.

7.3. Exclusion Criteria

The patient may not enter the trial if ANY of the following apply:

- Previous treatment for articular disease with DMARDs including, but not limited to, methotrexate, sulfasalazine, leflunomide and ciclosporin
- Female patient who is pregnant, breast-feeding or planning pregnancy during the course of the trial.
- Significant renal (estimated glomerular filtration rate <30ml/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
- Scheduled elective surgery or other procedures requiring general anaesthesia during the trial.
- Patient with life expectancy of less than 6 months.
- Any other significant disease or disorder which, in the opinion of the Investigator, may either 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 randomised to arm 3 and receiving adalimumab therapy:

- Active tuberculosis (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.

[1] Acceptable methods of contraception are:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, transdermal.
- progestogen-only hormonal contraception associated with inhibition of ovulation as the primary mode of action and also where it is not the primary mode of action: oral, injectable, implantable.
- intrauterine device (IUD).
- intrauterine hormone-releasing system (IUS).
- bilateral tubal occlusion.
- vasectomised partner.
- sexual abstinence*.
- male or female condom with or without spermicide.
- cap, diaphragm or sponge with spermicide.

* defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

8. TRIAL PROCEDURES

A schedule showing screening, recruitment and randomisation procedures is shown in appendix B.

8.1. Screening and Eligibility Assessment

Potential participants will be identified from the PsA cohort (MONITOR-PsA REC Ref 17/SC/0556) which is recruited from new referrals to the rheumatology service particularly those referred to the early arthritis

clinic. Patients will be identified and approached initially by their clinical care team and will be given brief information about the cohort. If they are interested, a full patient information sheet (PIS) and informed consent form (ICF) will be given to them and explained. If they are happy to consent to the observational study, then this can be performed on the same day. However as stated in 8.2, they will be allowed as much time as they wish to consider their participation.

As part of the consent process for the MONITOR-PsA cohort patients will be 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 randomised by the research team for an invitation to participate in these future interventional studies
3. For anonymized data to be used as comparison as a control group for these future interventional studies.

If they consent to the cohort and also 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 this study. If they are potentially eligible and have consented to be randomised to an invitation to participate in further interventional studies then they will be randomised either to remain in the cohort as a control subject or to be offered one of the two interventions. If they are randomised to be offered an intervention, further information will be given as detailed below in section 8.2 and appropriate time will be given for the participant to consider the invitation and discuss participation with friends/family.

Additional screening that is specific for arm 3 of the study (early use of TNF inhibitors) will require exclusion of active/latent TB and viral infections. These tests will only be performed after the patient has given informed consent to the trial for those randomised to that arm.

8.2. Recruitment

If participants are randomised to be offered the intervention then they will be approached initially by their clinical care team within the cohort study and will be given brief information about the intervention offered. If they are interested they will be given the full PIS for this intervention as well as a verbal explanation of the trial. They will be allowed as much time as they wish to consider their participation. If they decline to consent then they will be followed only in the cohort (in line with their previous cohort consent) assuming they are still happy for this. If, after they have had time to consider the proposal, they are happy to consent to the intervention, then they will be asked to sign the ICF prior to any study related procedures occurring including screening for tuberculosis and viral infections in the case of those randomised to arm 3.

8.3. Informed Consent

The participant must personally sign and date the latest approved version of the ICF before any trial specific procedures are performed.

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

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in

the trial. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator (CI/PI). A copy of the completed ICF will be retained by the participant. One copy will be sent to the study coordinating team in Oxford and one will be retained in the healthcare record. The original will be retained in the Investigator Site File (ISF).

The PIS will outline that the participants name and contact details (including mobile, phone and email), will be collected to facilitate follow up and full data collection. A copy will sent to the study coordinating team in Oxford using secure encrypted electronic transfer. These details may be used (with appropriate consent) by the study team to check contact details using the NHS digital and other central UK NHS bodies, and to provide other basic study-related information that may be needed for follow up and to allow possible telephone contact if they do not attend clinic visits.

The ICF will also ask for permission to allow access to participant data by responsible members of the University of Oxford or the NHS Trust for monitoring and/or audit of the study to ensure we are complying with regulations.

8.4. Randomisation, blinding and code-breaking

As described in section 8.1, randomisation will be carried out if participants have indicated a willingness to be contacted about and randomised into additional interventional trials and if they meet the inclusion/exclusion criteria based on the baseline cohort data collection.

Randomisation to the interventions will be 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 will ensure balanced allocations across the treatment groups. The following minimisation factors will be 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 will be randomised using simple randomisation to seed the minimisation algorithm which will have probabilistic element introduced to ensure unpredictability of the treatment assignment.

The randomisation process is a two stage procedure. The first stage is completed once a potential participant are known to be potentially eligible - see section 8.1 – and allocates the treatment arm. The second stage confirms consent and eligibility for this treatment arm. For participants allocated to arms 2 & 3, the second stage is to be complete once consent for the intervention and any additional required screening assessment have been completed.

The treatment received is open-label so there is no necessity for code breaking.

Clinical assessments will be performed by a blinded research nurse or metrologist with appropriate training.

8.5. Baseline Assessments

Baseline assessments must be performed before participants start on treatment. The following will be assessed for all participants within the cohort study so this data will already be available:

- Medical history
- Medication (glucocorticoids and non-steroidal anti-inflammatory drugs only)

- Physical examination: pulse; blood pressure; height; weight
- Safety bloods: haemoglobin, white blood count (WBC), platelet count, neutrophils, ALT.
- Antibody markers: anti citrullinated peptide antibody (ACPA) and rheumatoid factor (RF)
- Efficacy bloods: C-reactive protein (CRP)
- PsA history: PsA type; symptom onset; diagnosis date; peripheral and axial early morning stiffness (EMS); inflammatory back pain (IBP).
- Classification Criteria for Psoriatic Arthritis (CASPAR) Criteria:
    - Evidence of current psoriasis
    - Personal history of psoriasis
    - Family history of psoriasis
    - Psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis
    - Evidence of current or documented history of dactylitis
    - Rheumatoid factor negative
    - Evidence of new bone formation on radiographs.
- Full clinical disease assessment:
    - TJC and SJC: a full 68 tender and 66 swollen joint count will be performed. Replaced joints will not be counted
    - Dactylitis Assessment using count of tender dactylitic digits
    - Enthesitis Assessment using Leeds Enthesitis Index (LEI)[31] and Spondyloarthritis Research Consortium of Canada (SPARCC)[32] enthesitis index
    - Psoriasis Area Severity Index (PASI) and body surface area (BSA)
    - Physician's visual analogue scale (VAS) of overall disease activity
    - BASMI (only if clinical/imaging evidence of axial involvement)
    - Copies of radiographs will be saved for the modified Sharp-van der Heijde radiographic score for PsA [29] and PsA Ratingen Score (PARS) [30].

For arm 3 screening for tuberculosis and hepatitis infections, if not already available, will be carried out after consent to take part in the trial has been obtained. This requires an additional 15mls of blood to be taken.

Participants will be asked to complete the following patient reported outcomes:

- Global disease activity VAS
- Patient pain VAS
- Health assessment questionnaire (HAQ)[33]
- PsA impact of disease (PSAID)[34]
- BASDAI
- SF36[35]
- EQ-5D-5L[36]
- Work productivity and activity impairment (WPAI)[37]
- BASFI

The primary outcome is the PASDAS continuous outcome at 24 weeks. The PASDAS is a composite score including both clinical assessment and patient reported outcomes. It is calculated as (((0.18√physcian 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 (Leeds enthesitis index +1)) + (0.37 LN (tender dactylitis count+1)) + (0.102 x LN (CRP+1)) +2) x 1.5. The PASDAS score range is 0 to 10, with higher values indicating worse disease activity.

8.6. Subsequent Visits

Follow-up will be for one year with data to be collected at 12, 24, 36 and 48 weeks for this trial. Not all patients will complete the week 48 follow up assessments. Those patients recruited within the last 24 weeks of recruitment, will only have visit assessments conducted up to week 36 and will then revert to the MONITOR cohort.

Participants receiving the intervention will also be able to contact the trials team via a helpline if they require rescue therapy after week 24 of the trial. Participants will revert back to the cohort for longer term follow-up which will occur at least annually.

At each visit the following assessments will be performed in line with the cohort study:

- Medical history (update)
- Current treatment for psoriatic arthritis
- Concomitant medication history (glucocorticoids and non-steroidal anti-inflammatory drugs only)
- Treatment tolerability
- Physical examination: pulse; blood pressure; weight
- Safety bloods[1]: haemoglobin, WBC, platelet count, neutrophils, ALT.
- Efficacy bloods[1]: CRP and eGRF
- Full clinical disease assessment:
    - TJC and SJC: a full 68 tender and 66 swollen joint count will be performed. Replaced joints will not be counted
    - Dactylitis Assessment using count of tender dactylitic digits
    - LEI[31] and SPARCC[32] enthesitis index
    - PASI and BSA
    - Physician's VAS of overall disease activity

Participants will be asked to complete the following patient reported outcomes:

- Global disease activity VAS
- Patient pain VAS
- Health assessment questionnaire (HAQ)[33]
- PsA impact of disease (PSAID)[34]
- BASDAI
- SF36[35]
- Work productivity and activity impairment (WPAI)[37]
- Health system utilisation data
- Treatment satisfaction questionnaire for medication (TSQM)[28]
- BASFI
- Compliance with treatment

[1] See section 8.7 for details.

The primary outcome is the PASDAS continuous outcome at 24 weeks. The PASDAS is a composite score including both clinical assessment and patient reported outcomes. It is calculated as (((0.18√physcian global VAS) + (0.159√patient global VAS) – (0.253 x √SF12-PCS) + (0.101 x LN (SJC+1)) + (0.048 x LN (TJC+1)) + (0.23 x LN (Leeds enthesitis index +1)) + (0.37 LN (tender dactylitis count+1)) + (0.102 x LN (CRP+1)) +2) x 1.5.

At certain visits additional assessments will be performed:

- Week 24 and 48
    - EQ-5D-5L[36]
    - Health system utilisation data
- Week 48
    - Copies of radiographs will be saved for the modified Sharp-van der Heijde radiographic score for PsA [29] and PsA Ratingen Score (PARS) [30].
- Baseline and Week 48
    - BASMI (only if clinical/imaging evidence of axial involvement)

The following assessments must be carried out as face to face appointment to enable assessment of MDA and therefore implementation of treat to target:

- 12 weeks
- 24 weeks
  48 weeksNot all patients will complete the week 48 follow up assessments. Those patients recruited within the last 24 weeks of recruitment, will only have visit assessments conducted up to week 36. Investigational medicinal product (IMP) will be provided for these patients until week 32. A week 36 assessment will be completed which includes a safety assessment.

Participants week 48 Radiographs, EQ-5D-5L and Health system utilization data will be completed as part of the MONITOR cohort.

The 36 weeks assessment may be carried out as a remote visit if the participant is stable, their disease is under control and they have previously met target MDA and they are unable to be reviewed within the hospital. In this case, where available a web link for online completion will be sent by email, otherwise paper questionnaires will be provided to the participants to complete and return to the study site by post. Provision of drug supply for those receiving IMPs will be organized by the hospital and may involve a visit to the hospital to collect medication. A friend or relative may collect the medication if the participant is unable to collect it themselves.

However, should any future change in national or local government or NHS policy mean that those follow up visits detailed above as needing to be done face to face cannot be carried out as face to face appointments, then remote follow up of existing study participants should be carried out in preference to withdrawing the participant from the study.

8.7. Sample Handling

Routine safety and efficacy blood tests will be performed for all participants receiving disease-modifying therapy as done in standard NHS care. Monitoring will be arranged for each individual patient as per standard clinical practice dependent on the disease modifying therapy that they receive. This will follow national shared care guidelines for the management of DMARDs published by the British Society of Rheumatology. This states that FBC, ALT and U&Es should be checked every 2 weeks until on a stable dose for 6 weeks; then monthly for 3 months and then 3 monthly thereafter. The exception is for a combination of methotrexate and leflunomide where monthly blood monitoring should be extended for at least 12 months. As these blood tests are performed within standard NHS care, where changes from this standard national policy on blood monitoring are implemented by the NHS hospitals, this may change in accordance with local guidelines. For

example, if monitoring frequency is reduced due to NHS pressures (e.g., COVID-19 pandemic or shortage of equipment such as blood bottles), then monitoring should remain in line with local hospital policy. The results of the routine NHS blood tests at 3 monthly intervals will be recorded in the trial CRFs to monitor safety of the treatment and calculate composite measures of efficacy.

8.8. Discontinuation from trial treatment/Withdrawal of Participants from Trial.

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 including:

- Pregnancy
- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
- Significant protocol deviation
- 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

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.

8.9. Discontinuation of trial treatment in pregnancy

Should a trial participant become pregnant, the decision to stop or continue treatment lies with the treating Doctor who should take into account the information in the relevant SmPC(s). Methotrexate and leflunomide are contraindicated in pregnancy.

For reporting requirements see section 10.7.

8.10. Discontinuation/Withdrawal of a site

Recruitment and screening data will be monitored by the trial team. This will also be reviewed by the Trial Management Group (TMG) and the Trial Steering Committee (TSC). Where necessary, after appropriate support, if a site has persistent low recruitment a site may be required to close and resources used to establish another site.

8.11. Definition of End of Trial

The end of study is the date of the last visit of the last participant, and all data has been entered and queries resolved.

9. INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

9.1. IMP Description

All IMPs are commercially available products routinely used in patients with PsA. Generic ('off the shelf') commercial supplies are to be used for methotrexate, sulfasalazine and leflunomide as determined by individual hospital sites. Methotrexate, sulfasalazine and leflunomide will be off the shelf supplies. There is no requirement to ring-fence off the shelf general hospital supplies of these IMPs. Pharmacy will be responsible for labelling the IMPs in accordance with the requirements of the Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994.

Adalimumab is supplied as an IMP by Abbvie for specific use within this trial as it is to be prescribed outside NICE approved use.

Formulation and storage of IMPs are in line with the manufacturers' recommendations. For further details refer to the SmPC for each IMP. A reference copy can be found in the Investigator and Pharmacy Site Files.

Abbvie will provide labels for trial- specific adalimumab for use in accordance with the requirements of the Medicines for Human Use (Clinical Trials) Regulations 2004 (and amended in 2006). For methotrexate, sulfasalazine and leflunomide Regulation 46 (2) of SI 2004/1031 will apply so sites are only required to apply a dispensing label. The pharmacy at each NHS site will be responsible for applying the labels for stock drugs in accordance with the above legislation.

Methotrexate
Methotrexate is considered one of the group of synthetic disease-modifying anti-rheumatic drugs and the most commonly prescribed first line therapy in PsA. It is an immune suppressant licensed for the treatment of psoriasis and rheumatoid arthritis. Common side effects include nausea, fatigue, mouth ulcers, raised liver enzymes and leucopenia. It is given orally or subcutaneously in doses from 5-25mg per week. Methotrexate will be prescribed for both interventional trial arms as the first line therapy either concomitantly with another DMARD (in arm 2) or adalimumab (in arm 3). It is the most commonly prescribed first line treatment for PsA and is also used as the default first line therapy for all patients in the clinic (and therefore the control group). It will be prescribed at 15mg per week for the first 4 weeks, 20mg per week for the next 4 weeks and 25mg per week thereafter as tolerated.

Sulfasalazine
Sulfasalazine is considered one of the group of synthetic disease-modifying anti-rheumatic drugs and is one of the commonly prescribed second line therapies in PsA. It is an immune suppressant licensed for the treatment of rheumatoid arthritis. Common side effects include nausea, fatigue, rash and leucopenia. It is given orally in doses from 500mg-3g daily in two or three divided doses. It is one of the second line DMARDs that may be used in combination with methotrexate in arm 1 of the trial. It will be prescribed with a standard increasing dose over the first 4 weeks aiming for an initial dose of 1g orally twice per day with the potential to increase up to 40mg/kg/day.

Leflunomide
Leflunomide is considered one of the group of synthetic disease-modifying anti-rheumatic drugs and is one of the commonly prescribed second line therapies in PsA. It is an immune suppressant licensed for the treatment of PsA. Common side effects include nausea, fatigue, diarrhoea and raised liver enzymes. It is

given orally in doses from 10-20mg daily. It will be prescribed at an initial dose of 10mg per day with the potential to increase to 20mg per day if disease is not controlled.

Adalimumab
Adalimumab is considered one of the group of biologic disease-modifying anti-rheumatic drugs and is one of the commonly prescribed biologic therapies in PsA. It is a humanised monoclonal antibody directed against TNF alpha. It is an immune suppressant licensed for the treatment of PsA in patients who have failed synthetic DMARDs. Common side effects include increased frequency of infections, headache, injection site reaction, skin rash, sinusitis and antibody development. It is given by subcutaneous injection at a dose of 40mg every other week.

9.2. Storage of IMP

Formulation and storage of IMPs are in line with the manufacturers' recommendations. For further details refer to the SmPC for each IMP. A reference copy can be found in the Investigator and Pharmacy Site Files. Clinical supplies must be received by a designated person at the study site, handled and stored safely and properly in accordance with standard pharmacy procedures. Supply of adalimumab for participants in arm 3 of this study will be specific study drug supply which will be kept separately from usual hospital drug supplies in accordance with trial procedures. This will be kept in a secured location to which only the investigator and designated assistants have access. Clinical supplies are dispensed in accordance with the protocol.

9.3. Compliance with Trial Treatment

Non-compliance will be assessed at each clinical trial visit and any missed doses reported by the participants will be recorded.

9.4. Accountability of the Trial Treatment

Methotrexate, Sulfasalazine and Leflunomide
Methotrexate, sulfasalazine and leflunomide will be off the shelf supplies. There is no requirement to ring-fence off the shelf general hospital supplies of these IMPs. Pharmacy will be responsible for labelling the IMPs in accordance with the requirements of the Medicines for Human Use (Marketing Authorisations Etc) Regulations 1994. Non-compliance will be assessed at each clinical trial visit and any missed doses reported by the participants will be recorded.

Adalimumab
Pharmacy is responsible for keeping accurate records of the clinical supplies, the amount dispensed to and returned by the subjects, and the disposition at the end of the study.

Clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Clinical supplies are dispensed in accordance with the protocol.

The investigator will be responsible for the destruction of the supplies at the study centre pursuant to local regulations, and the investigator's institutional policies.

9.5. Concomitant Medication

There are no specifically excluded concomitant medications although some drugs are contraindicated alongside IMPs in this protocol (e.g. sulphonamides). Any new therapies for other conditions should only be prescribed if safe alongside their DMARD therapy. Participants and their GP will be aware of participants'

treatments as this trial is open label. We expect that the majority of participants will take non-steroidal anti-inflammatory drugs or other analgesics for joint pain and the doses of these will be recorded.

9.6. Post-trial Treatment

All therapies used within this trial are routinely used in NHS practice. Any participant who has responded well to a standard DMARD IMP (methotrexate, leflunomide, sulfasalazine) in the study will be eligible to continue with these as standard NHS supply. Participants receiving adalimumab as an IMP in this study will not fulfil the standard National Institute for Health and Clinical Excellence (NICE) funding requirements for ongoing TNF inhibitor therapy. If participants on treatment arm 3, flare following withdrawal of adalimumab after week 24 of the study, they would have to trial a second DMARD prior to being eligible for ongoing TNF inhibitor therapy.

10. SAFETY REPORTING

10.1. Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the

	event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product.

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

Any pregnancy occurring during the clinical trial and the outcome of the pregnancy should be recorded and followed up for congenital abnormality or birth defect, at which point it would fall within the definition of "serious".

10.2. Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

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

10.3. Procedures for Recording Adverse Events

All adverse events will not be collected in this trial as all the IMPs are licenced, currently used in PsA and have well documented safety profiles. Only adverse events of special interest (either extra-articular manifestations of the disease or those likely to be related to the therapy used for PsA) occurring during the study will be collected at each study visit by patient questionnaire and physician report as below:

- Patient reported
    - Nausea/vomiting
    - Heartburn/dyspepsia
    - Diarrhoea
    - Fatigue
    - Hair loss
    - Injection site reaction
- Physician reported
    - Infections
    - Liver function test abnormalities
    - Neutropenia/leucopenia
    - Uveitis

The following information will be recorded: date of onset and end date, severity, assessment of relatedness to trial medication and action taken. The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe. Follow-up information should be provided as necessary.

It will be left to the Investigator's clinical judgment to decide whether or not an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant would be asked to continue follow up for the study. If they also withdraw from all trial follow up, we would request that they undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

10.4. Reporting Procedures for Serious Adverse Events

All SAEs occurring during the trial and until 4 weeks after the final visit that are observed by the Investigator or reported by the participant, will be recorded and reported to the Trials Unit on a trial-specific SAE Form.

All SAEs must be reported on the SAE reporting form to the study team at OCTRU within 24 hours of the Site Study Team becoming aware of the event. They will perform an initial check of the report, request any additional information, and ensure it is reviewed by a Nominated Person. All SAE information must be recorded on an SAE form and scanned and emailed to OCTRU. Additional and further requested information (follow-up or corrections to the original case) will be detailed on the same SAE form (where changes are signed and dated) or on a new SAE Report Form (if too many changes) and emailed to OCTRU.

10.5. Expectedness

Events will also be assessed for expectedness according to the RSI section of the Summary of Product Characteristics for each IMP assessed as 'related'. The relevant SmPC for each IMP in question will be selected. Assessment of expectedness will be performed centrally by OCTRU in collaboration with the Nominated Person for the trial who will be identified in accordance with the OCTRU Standard Operating Procedure (SOP).

10.6. SUSAR Reporting

All SUSARs will be reported by the OCTRU on behalf of the CI to the relevant Competent Authority and to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after OCTRU is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

PIs in this trial will be informed of all SUSARs occurring in this trial.

10.7. Reporting Procedure for Pregnancy

Should a pregnancy occur in a trial participant randomized to Arm 2 or 3 of the trial, the pregnancy must be reported to the Study team at OCTRU via completion of the study specific Pregnancy Notification Form which must be completed and scanned, then emailed to OCTRU as soon as possible.

Should a pregnancy occur in the partner of a trial participant randomized to Arm 3 of the trial (adalimumab), the pregnancy must be reported to the Study team at OCTRU. Prior to completion of the study specific Pregnancy Notification Form, consent for data collection must first be obtained from the pregnant partner using the SPEED pregnancy information and consent form. The name and contact details of the pregnant partner should be requested from the trial participant and a copy of the SPEED pregnancy information and consent form provided to the pregnant partner. Consent from the pregnant partner should be obtained promptly, ideally within 2 weeks, if the partner is happy to consent. Once consent is obtained the Pregnancy Notification Form must be completed and scanned, then emailed to OCTRU as soon as possible. If consent is not provided, the pregnancy notification form will not be completed and any personal data of the partner will be immediately destroyed.

The PI must ensure that the outcome of the pregnancy is known and reported to OCTRU (unless in the case of a pregnant partner consent is not provided). In the event of a congenital abnormality or birth defect, this must be reported as a serious adverse event.

See section 8.9 for information about discontinuation of study treatment in the event of pregnancy.

10.8. Reporting Obligations to AbbVie

Following receipt of an SAE form or pregnancy notification form relating to a participant in Arm 3 of the trial (adalimumab), the study team at OCTRU shall within 24 hours of learning of the event report to AbbVie:

a) All pregnancies and all SAEs experienced by a study subject receiving an AbbVie product regardless of the relationship of the event to the AbbVie product.

b) Any subjects receiving an AbbVie Product whose pregnancy has resulted in a negative outcome or untoward event during the course of pregnancy or upon delivery.

c) Any pregnancies experienced by a partner of a study subject receiving an AbbVie product.

d) Escalate any Safety Signals within 15 calendar days of identification.

Any requests from AbbVie for further information will be sent to the relevant site staff by the study team at OCTRU, to whom the requests must be returned. The study team at OCTRU will be responsible for sending on such information to AbbVie. The SAE forms that will be sent to AbbVie do not contain any identifiable data.

In addition, the study team at OCTRU will copy AbbVie on the submission to the country regulatory agency of events meeting the definition of an expedited safety report at the time of submission to the agency.

10.9. Data Safety and Monitoring Committee

A Data Safety and Monitoring Committee (DSMC) will be appointed to safeguard the interests of the trial participants to assess the safety and efficacy of the interventions during the trial, and to monitor the overall conduct of the trial, protecting its validity and credibility. The DSMC will be independent of the trial investigators and sponsor and will adopt a charter that defines its terms of reference and operation in relation to oversight of the trial. It will meet at least every 12 months over the duration of the trial. The DSMC will not be asked to perform any formal interim analyses of effectiveness. It will, however, review accruing data and summaries of that data presented by treatment group and will assess the screening algorithm against the eligibility criteria. It will also consider emerging evidence from other related trials or research and review any related SAEs that have been reported. The DSMC may advise the chair of the TSC at any time if, in its view, the trial should be stopped for ethical reasons, including concerns about participant safety or clear evidence of the effectiveness of one of the treatments. The DSMC will comprise an independent medically qualified clinician, statistician, and other researchers.

The DSMC for this study will also cover the cohort study MONITOR-PsA to allow cohesive review of any safety issues in this TWiCs study.

10.10. Development Safety Update Reports

The DSUR will be submitted in accordance with the OCTRU SOP, on behalf of the CI, once a year throughout the clinical trial, or on request, to the MHRA, REC, HRA (where required), and Sponsor.

10.11. Product complaints (Adalimumab)

The sites shall report to the study team at OCTRU any suspected quality defect in an AbbVie Product or its AbbVie-provided packaging, labelling, or medical device component (collectively, “Product Complaint”). The sites will report Product Complaints that involve an AbbVie Product, whether AbbVie has supplied the AbbVie Product used in the Study or not. Product Complaints may include, but are not limited to:

- Damaged or broken product or packaging issues,
- Product appearance whose colour/markings do not match the labelling,
- Missing component/product,
- Device not working properly or use errors,
- Any illness, injury, or adverse event in the proximity of the device,
- An adverse event that could be a result of using the device,
- Any event needing medical or surgical intervention, including hospitalization, while using the device,
- Any death of a patient using a device.

The study team at OCTRU will forward the complaints to AbbVie within 24 hours of receipt.

11. STATISTICS

Full details of the statistical analysis will be provided in a separate statistical analysis plan (SAP) which will be drafted early in the trial and finalised prior to the primary analysis data lock. Stata (StataCorp LP) or other appropriate validated statistical software will be used for analysis. A summary of the planned statistical analysis is included here.

11.1. Description of Statistical Methods

The primary outcome is the PASDAS score at 24 weeks.

The PASDAS formula is calculated using a combination of clinician and patient reported items: (((0.18√physcian 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. The PASDAS score range is 0 to 10, with higher values indicating worse disease activity.

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 in the PASDAS score at week 24 between any of the three treatment arms. Only if this is significant at the 5% level will we proceed to the next analysis comparing each intervention against the control cohort with the following null hypotheses:

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

Both of these will be tested at 5% significance (with no adjustment for multiple testing). If both are significant, then we will move to comparing the two interventional arms at a reduced significance level.

The primary outcome, PASDAS score at 24 weeks, will be analysed using linear regression and estimates for the difference between groups will be presented with the corresponding 95% confidence interval. Additional analyses will be undertaken using multi-variable linear regression (for continuous outcomes) or logistic regression (for binary outcomes) adjusting for randomisation factors and baseline PASDAS score. Complier average causal effect (CACE) analysis will also be undertaken to take into account compliance to the treatments for the primary outcome analysis.

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 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

A PASDAS good response is defined as a reduction in PASDAS score (on a continuous scale) from baseline of ≥1.6 and a final PASDAS score of ≤3.2 as shown in the table below. A PASDAS moderate response is as detailed below.

	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

- PSAID score (on a continuous scale) at 24 and 48 weeks.

This patient reported outcome measure will be scored in line with the scoring manual[34].

Exploratory outcomes will include: progression in joint damage as measured by change in radiographic score (change in modified Sharp-van der Heijde total and erosion scores from 0 to 48 weeks) following withdrawal of TNF inhibitor.

Statistical analyses for key secondary endpoints will include multilevel mixed-effects logistic or linear regression models to take into account the binary or continuous outcomes collected at the follow-up assessments. Models will be adjusted for baseline measures of the relevant outcome, as well as stratification factors and taking into account a time by treatment interaction term. A hierarchical method of testing, as described for the primary outcome measure will be used.

Additional outcome measures will be summarised descriptively at the relevant follow-up time points using mean and standard deviation or median and interquartile range, as appropriate, for continuous outcomes, and frequency and percentages for categorical outcomes. Statistical tests such as analysis of variance or chi-squared tests will be used where appropriate, using the hierarchical method of testing as described above.

11.2. Health Economics analysis

The economic evaluation will estimate the cost effectiveness of 1. standard step up therapy in the cohort vs early combination DMARD, 2. standard step up therapy in the cohort vs early TNF inhibitor therapy and 3. early combination DMARD vs early TNF inhibitor therapy in adults with moderate or severe PsA. Direct medical cost from the trial will be collected at the end of the trial (at 48 weeks post randomisation) using national databases such as the British National Formulary (BNF). Primary, Community and Social care service use will be collected at 24 weeks and 48 weeks post randomisation using patient self-reported questionnaires. Note that for those patients recruited within the last 24 weeks of recruitment will not have generated week 48 data as part of SPEED, but this data will be collected as part of the MONITOR cohort study. Where data is missing, please refer to section 11.6. Data collected will also record indirect costs as well as direct non-medical costs. Unit cost data will be obtained from national databases such as the BNF and PSSRU Costs of Health and Social Care[39].

HRQoL will be estimated using the EuroQol (EQ-5D-5L[36]). Trial participants will be asked to complete EuroQol (EQ-5D) at baseline, 24 weeks and 48 weeks post randomisation. Responses to the EQ-5D will be converted into multi-attribute utility scores using established algorithm[40, 41]. A within trial evaluation will be conducted from a UK NHS and Personal Social Services perspective (PSS) using the trial data[42]. The outputs of the cost-effectiveness analysis will be presented in terms of expected Incremental Cost Effectiveness Ratios (ICERs); $\Delta Costs/\ \Delta QALY$, where , $\Delta Costs$ is the difference in total costs between the interventions and $\Delta QALY$ is the difference in utility between interventions), Cost Effectiveness Acceptability Curves (CEACs) generated via non-parametric bootstrapping to present the probability of the intervention being cost-effective for given thresholds for costs per QALY gained as well as Expected Net Benefit [incremental health gain x pay threshold)- incremental cost]. Further, sensitivity analyses will be conducted to explore uncertainties surrounding key parameters in the economic evaluation and to consider the broader issue of the generalisability of the study results. Regression analysis will be used to estimate the between-group differences in mean costs and Quality Adjusted Life Years (QALYs), adjusting for centre, sex, age and other baseline differences among the three trial arms.

If the intervention is shown to be effective in controlling disease progression at 48-weeks follow-up, a long-term economic model that evaluates the cost-effectiveness of 1. standard step up therapy in the cohort vs

early combination DMARD, 2. standard step up therapy in the cohort vs early TNF inhibitor therapy and 3. early combination DMARD vs early TNF inhibitor therapy in adults with moderate or severe psoriasis arthritis will be constructed. Costs, utilities and transition probabilities for this model will be obtained from the trial and the published literature.

11.3. The Number of Participants

The primary outcome is the PASDAS score (on a continuous scale) 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.

A change to the way the primary outcome is specified has been implemented. By using the PASDAS score on the continuous scale rather than as a binary outcome of those achieving a good response. 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, 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 [43]. The standard deviation is based on the observed variability in the continuous PASDAS score in the MONITOR cohort [44]

11.4. The Level of Statistical Significance

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).

11.5. Criteria for the Termination of the Trial

In the light of the interim data and other evidence from relevant studies, the DSMC will inform the TSC if there is proof beyond reasonable doubt that the data indicate the trial should be terminated or evidence of safety concerns. A decision to inform the TSC of such a finding will in part be based on statistical considerations (appropriate proof beyond reasonable doubt cannot be specified precisely). Both the DSMC and TSC will follow appropriate charters drawn up prior to the start of the trial as per OCTRU standard operating procedures.

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

Missing data will be minimised by careful data management. Missing data will be described with reasons given where available; the number and percentage of individuals in the missing category will be presented by treatment arm. All data collected on data collection forms will be used, since only essential data items will be collected. No data will be considered spurious in the analysis since all data will be checked and cleaned before analysis.

The nature and mechanism for missing variables and outcomes will be investigated, and if appropriate multiple imputation will be used. Sensitivity analyses will be undertaken assessing the underlying missing data assumptions. Any imputation techniques will be fully described in the Statistical Analysis Plan.

11.7. Inclusion in Analysis

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.

In order to take into account the different treatment regimens and compliance, complier average causal effect (CACE) analysis will be used for this TWiCs trial.

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

A detailed statistical analysis plan will be drawn up prior to patient recruitment or early in the trial with review and appropriate sign-off following OCTRU SOPs. Any changes to the statistical analysis plan during the trial will be subject to the same review and sign-off procedure with details of changes being included in the new version. Any changes/deviations from the original SAP will be described and justified in protocol and/or in the final report, as appropriate.

12. DATA MANAGEMENT

12.1. Source Data

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

CRF/eCRF entries will be considered source data if the CRF/eCRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed ICF, the participant will be referred to by the trial participant number/code, not by name.

12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections. All data and documentation will be stored in accordance with regulatory requirements and access to the data will be restricted to authorised study personnel. OCTRU will securely hold the database.

12.3. Data Recording and Record Keeping

All trial data will be entered on to an eCRF as part of the MONITOR-PsA cohort study. Participants (both in the interventional group and the control group) of this study will be clearly identified on this database.

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

Data collection will be performed alongside clinical NHS appointments and data will be inputted directly to the electronic clinical record form (eCRF).

Baseline data will be collected from participants and/or the research team and recorded on eCRF. Data will also be collected for the study follow up time frames, and will be via eCRF or via telephone call for collection

of core data. Where telephone follow up is used, a member of the central study team will carry out data collection directly onto the follow up eCRF. If a patient appointment is carried out remotely and questionnaires are to be completed online, an email will be sent containing a weblink to complete the questionnaires online directly into a study database (see below for details of the databases). Alternatively participants can be sent paper questionnaires, which will be labelled with their initials and trial ID only, and asked to return them to the site team by post once completed

Upon receipt of questionnaires/CRFs, appropriate data quality and validation checks will be carried out.

Study documentation will be retained for a minimum of 15 years after completion of study-related activities. Collaborating sites are delegated the responsibility of archiving local essential documents (including the ISF) in an appropriate secure environment. The study office will archive the central Trial Master File (TMF) and associated documents according to University of Oxford policy and this may include the use of an external professional archiving site.

All data will be processed in compliance with applicable data protection legislation, and all documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed ICF, the participant will be referred to by their study number/code, not by name. Identifiable contact information will be stored separately from study data.

All sites except Cambridge & Bath: Participants will complete their PROMs on a tablet computer using a software developed by the OCTRU called LimeSurvey. This will securely store the data on a secure server within a university of Oxford facility alongside data entered by the healthcare tea. Patient level permissions will allow access to their data only. Clinical history, examination and medication data will be recorded directly into the same system by the clinical assessor. When questionnaires are complete online by participants having remote visits, participants will be emailed a weblink and asked to enter their participant ID to enable access to the secure database website.

Bath: Participants will complete their PROMs on a tablet computer using a software called Meridian developed for the Royal National Hospital for Rheumatic Diseases (RNHRD). This will securely store the data on a secure server within the locked Rheumatology Department's Facilities at the RNHRD alongside data entered by the healthcare team. Patient level permissions will allow access to their data only. Clinical history, examination and medication data will be recorded directly into Meridian by the clinical assessor. When questionnaires are complete online by participants having remote visits, participants will be emailed a weblink and required to enter their name and date of birth to enable access the secure database website. The entirety of the study-related clinical data can be securely sent from Meridian to the sponsor in Oxford for storage and analysis.

Cambridge: Participants will complete their PROMs on a tablet computer using a software called MyChart, that is an extension of EPIC; a fully integrated electronic patient record system. MyChart transmits PROMS data securely to EPIC. Clinical history, examination and medication data will be recorded directly into EPIC by the clinical assessor. The entirety of the study-related clinical data can be securely sent from EPIC to the sponsor in Oxford for storage and analysis. EPIC and MyChart are regulated by the Caldicott Guardian and Data Protection Officer at Cambridge University Hospitals NHSFT. When questionnaires are complete online by participants having remote visits they use the OCTRU LimeSurvey system (see above).

Data will be transferred to OCTRU as the coordinating centre from other centres via the secure e-CRF. Any other material transferred (e.g. consent forms) will be done using secure encrypted data transfer portals in compliance with OCTRU SOPs.

A data management and sharing plan is in place which will fully explain all aspects of data management.

During and after the end of the study pseudo-anonymised study datasets will be created and stored for the duration of the archive period, and may be shared with the funder, other researchers upon request and/or uploaded into a research data repository. Participants will not be identified from this data as only their study identifier will be provided. Following the end of the archive period (at which point the link to personal identifiers will no longer exist) these data sets would be de-identified study datasets and may therefore be stored indefinitely.

13. QUALITY ASSURANCE PROCEDURES

The trial will be conducted in accordance with the current approved protocol, Principles of GCP, relevant regulations and standard operating procedures, as per OCTRU requirements. Prior to the trial starting there will be a risk assessment and a specific risk-adopted monitoring plan drawn up for the trial. There will be focused central monitoring and where indicated as specified by OCTRU's SOPs there will be site monitoring activities too.

13.1. PROTOCOL DEVIATIONS

A trial related deviation is a departure from the ethically approved trial protocol or other trial document or process (e.g. consent process or IMP administration) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the trial master file. OCTRU SOPs define the procedure for identifying non-compliances, escalation to the trial management team and assessment of whether a non-compliance /deviation may be a potential Serious Breach.

13.2 SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as "A breach of GCP or the trial protocol which is likely to affect to a significant degree –

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

(b) the scientific value of the trial".

In the event that a serious breach is suspected, the trial team will contact the Sponsor without delay according to OCTRU's SOP. In collaboration with the CI, the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC, MHRA and the NHS host organisation within seven calendar days.

OCTRU SOPs define the procedure to be followed in the occurrence of a potential serious breach.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles the Declaration of Helsinki.

14.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

14.3. Approvals

The protocol, ICF, PIS and any proposed advertising material will be submitted to an appropriate REC, HRA, MHRA, and host institution(s) for written approval.

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

14.4. Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisation and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

14.5. Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all trial documents and any electronic database, with the exception of the CRF/eCRF, where participant initials may be added. All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial will comply with the applicable data protection legislation, which requires data to be anonymised as soon as it is practical to do so. Electronic data transfer will be encrypted means. If the questionnaires are completed online, this will be through one of the secure databased systems mentioned in section 10.3. Participants who opt for online completion will be sent a link and asked to enter their participant ID. The postal questionnaires will only be identified by participant ID and initials and no identifiable information will be included on the completed questionnaires which are to be returned to the site team by post.

14.6. Expenses and Benefits

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

14.7. Other Ethical Considerations

Vulnerable participants and participants who are not unable to consent for themselves will not be recruited to this study.

15. FINANCE AND INSURANCE

15.1. Funding

This study was originally funded by a National Institute of Health Research Clinician Scientist Award for Dr Laura Coates (ref CS-2016-16-016) through the University of Oxford with subsequent additional funding from Janssen-Cilag Ltd, UCB Biopharma SRL and AbbVie Ltd through the University of Oxford.

15.2. Insurance

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

16. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the NIHR. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

17. REFERENCES

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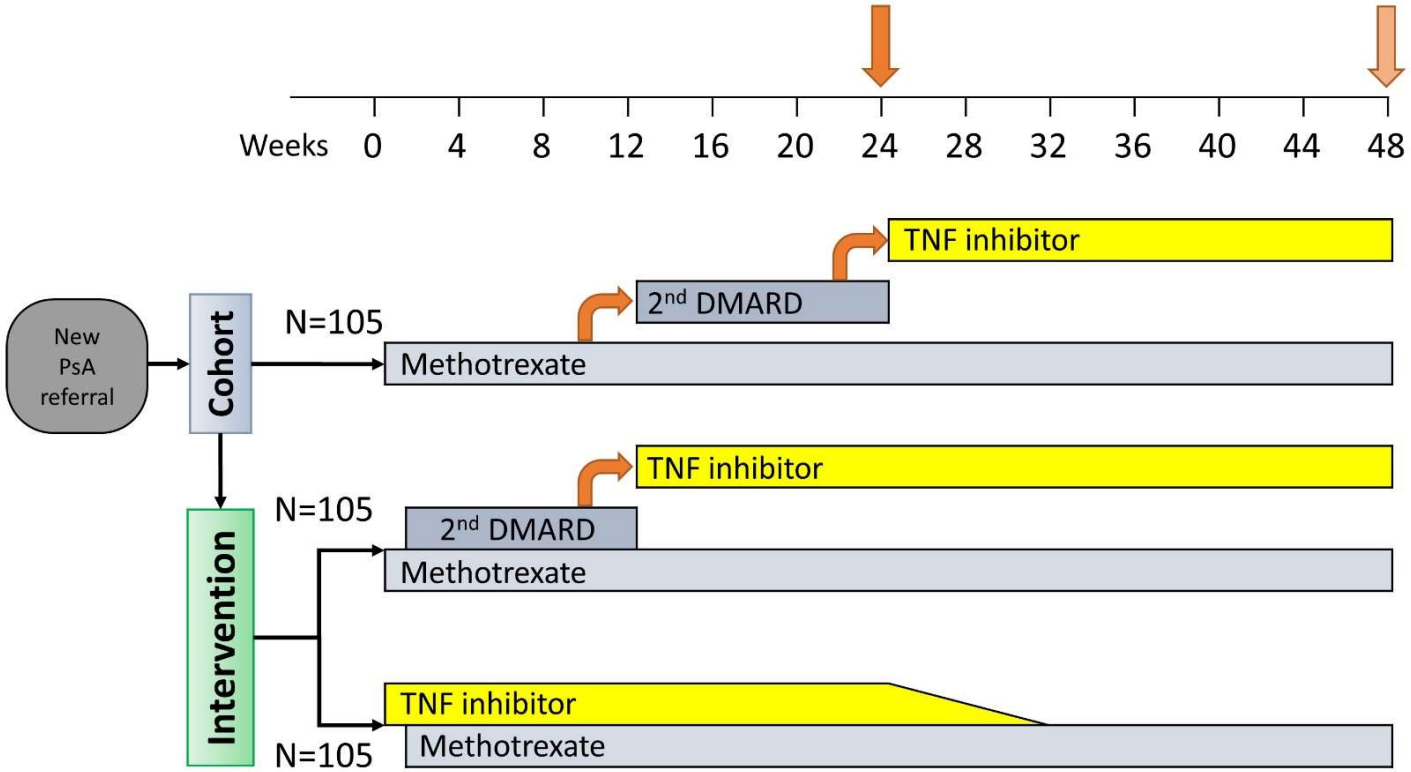
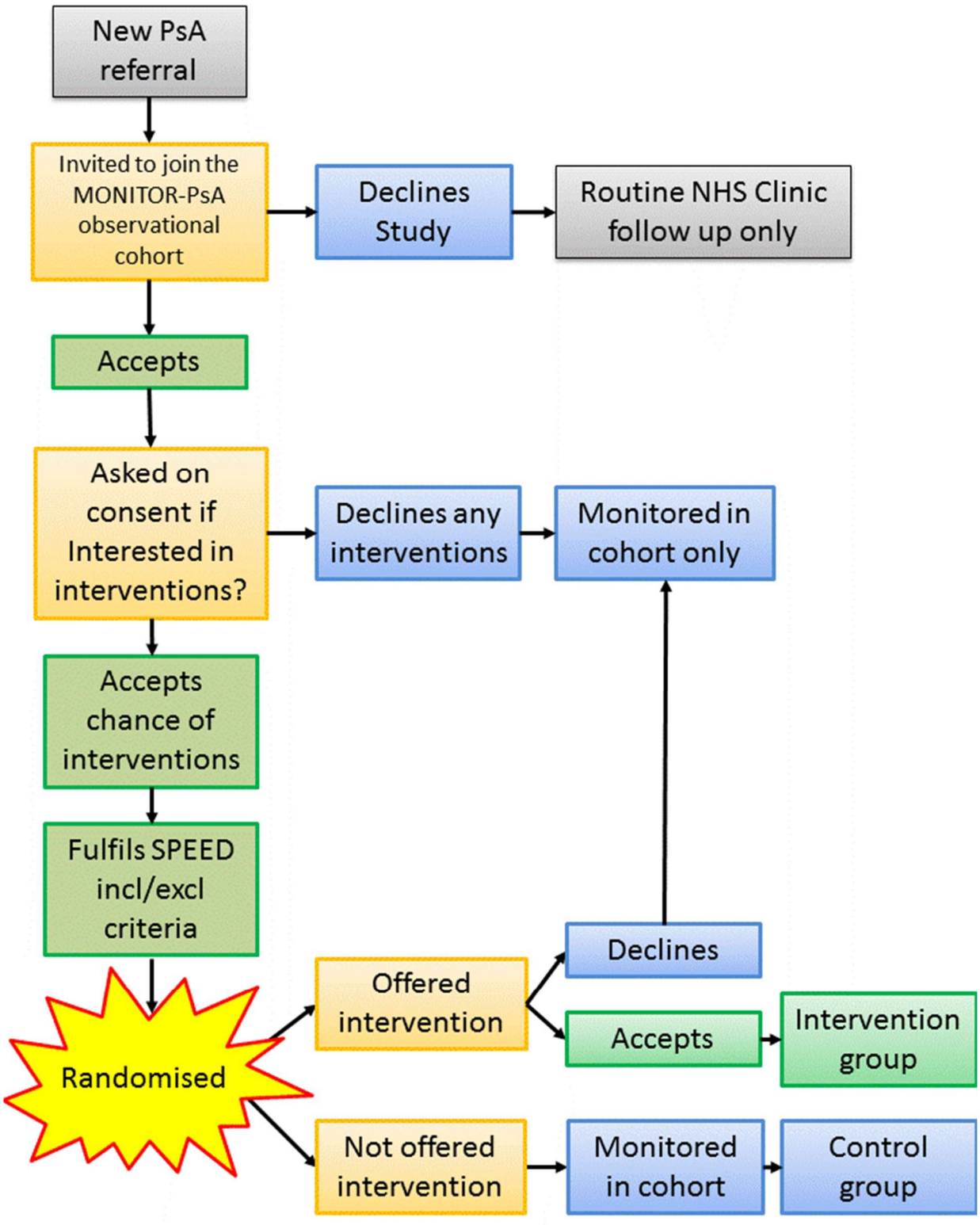
18. APPENDIX A: TRIAL FLOW CHART



19. APPENDIX B: SCREENING AND RECRUITMENT PROCEDURES



20. APPENDIX C: SCHEDULE OF PROCEDURES

Procedures	Baseline cohort/ Trial Screening	Visits				
		Baseline				
	Week -4 to 0	Week 0	Week 12	Week 24	Week 36 #	Week 48
Informed consent	X					
Demographics	X					
Medical history	X	X	X	X	X	X
Inclusion/exclusion criteria assessment	X					
Medication	X	X	X	X	X	X
Physical examination	X	X	X	X	X /^	X
Routine blood tests (FBC, U&Es, LFTs, CRP)**	X	X	X	X	X	X
Immunology (RF, ACPA)	X					
Radiographs of hands/feet/spine*		X				X
TB and hepatitis screening	X					
Eligibility assessment	X	X				
Randomisation	X					
Dispensing of drugs within Medication		X	X	X	X	
Adherence			X	X	X	X
68/66 Joint count		X	X	X	X / ^	X
Leeds and SPARCC enthesitis indexes		X	X	X	X / ^	X
Dactylitis count		X	X	X	X / ^	X
Psoriasis assessment (PASI and BSA)		X	X	X	X / ^	X
Physician VAS		X	X	X	X/ ^	X
Metrology with BASMI (if axial involvement)		X				X
Patient questionnaires (VAS, HAQ, SF36, PsAID, WPAI, BASDAI, BASFI)		X	X	X	X	X
TSQM questionnaire			X	X	X	X
EQ-5D-5L questionnaire		X		X		X
Healthcare utilisation data				X		X
Adverse event assessments		X	X	X	X / #	X

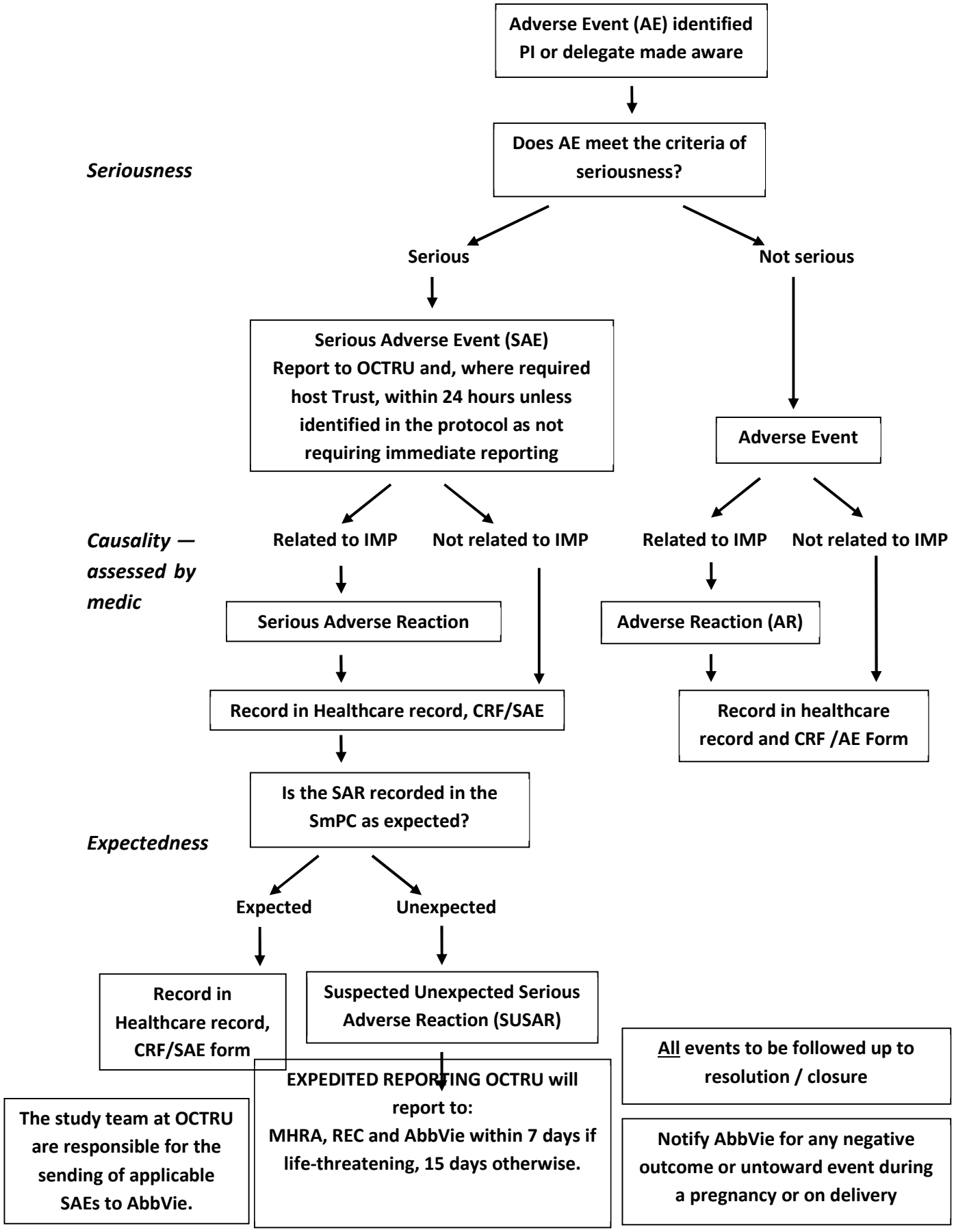
*Radiographs will be obtained from patient healthcare record.

**For information on routine blood tests please refer to section 8.7

The 36 week visit has been marked with a hash sign which signifies that the appointment can be carried out remotely if the participant is stable, their disease is under control, has previously met MDA target and are unable to be reviewed at hospital. Some of the physical assessments in this instance would be missing such as physical examination, joint counts, enthesitis, BASMI and dactylitis assessments, please see all assessments which could potentially be missing as being marked with a '^' symbol.

Note: Not all patients will complete the week 48 follow up assessments. Those patients recruited within the last 24 weeks of recruitment, will only have visit assessments conducted up to week 36 and then will revert to the MONITOR cohort.

21. APPENDIX D: SAE REPORTING FLOW CHART



22. APPENDIX E: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
N/A	1.0	08 Feb 2018	N/A	Submission version to HRA and MHRA
N/A	2.0	21 Mar 2018	L Coates	Response to MHRA Grounds for Non Acceptance
N/A	3.0	05 Apr 2018	L Coates, Y Sinomati	Response to REC review
1	4.0	18 Jul 2018	L Coates	Change in sampling handling to BSR guidelines for management of DMARDs. The phone number for Dr Laura Coates has been updated. The 'Health and Social care information Centre' wording has changed to the 'NHS Digital' on page 18 under the 'Informed Consent' section. The Sponsor address on the front page and Sponsor address in the Key Trial Contacts section has also changed to the Boundary House address
2	5.0	21 Mar 2019	L Coates, Y Sinomati	Changes to Data Protection, addition of Coventry and Newcastle sites, name changed from Concomitant Medication to Medication CRF which is referenced throughout the text and in Appendix C. Reference of BASMI removed from each of the patient visits to only be performed at baseline, 48 weeks and yearly thereafter, BASMI section of appendix C updated. The two new sites will be using OCTRU's systems under the data recording section.
3	6.0	08 Apr 2019	L Coates, M Watson	Clarification of labelling responsibilities for trial-specific stock
4	7.0	24Jun2020	Y Sinomati	Removal of study sites section on page 5 as it is a duplication of sites. In the sites section the hospital addresses have been updated. Trial design section 6 updated and Subsequent visits section 8.6: The participant assessment at 36 week can be completed remotely if the participant is stable, their disease is under control, they have previously met target MDA and they are unable to be

				reviewed within the hospital as opposed to the participant attending for a face to face clinic visit. Appendix C: The schedule of study procedures has been updated to reflect this and a footnote has been added to refer to the sample handling section 8.7. Inclusion criteria section 7.2, clarification provided for baseline. Section 8.4 correction to non-sensical sentence to read 'Clinical assessments will be performed by a blinded research nurse or metrologist with appropriate training'. Added a reference to Section 8.6 'see section 8.7 for details'. Causality, section 10.2 updated to match trial SAE form. Changes to Abbvie email address for reporting adverse events, safety signals and other correspondence and complaints. Minor typographical corrections. Additional abbreviations added to in section 3.
5	8.0	01Sep2021	Y Sinomati	The end of the Planned trial period changed to September 2023.
6	9.0		L Coates A Francis	A list of PIs removed on pages 1 and 2 TSC chair name and email address updated List of sites removed and '5-15 sites' added Section 1 – new address for sponsor added Planned trial period to end in July 2023. Section 4.1 'Proposed interventions' for Arm 2 and 3 updated for clarity and the definition of participant intolerance to the drugs. Section 4.2 'Methotrexate' updated for clarity Section 5 – Outcome and objective measures table has been clarified.

				Section 6 – removal of wording 'following withdrawal of their adalimumab treatment after week 24'. Section 7.2 'Inclusion criteria' – blood results required within 12 weeks rather than 28 days to be in line with current clinical practice. Section 7.3 'Exclusion criteria' - acceptable methods of contraception are listed for patients in the trial. Section 8.4 – 'Of 0.8' has been removed as per statistician requirement. Section 8.7 'Sample handling' Clarification on blood monitoring to be in line with NHS practice. Section 8.9 'Discontinuation of trial treatment in pregnancy', statement added for patients who become pregnant as to whether to stop or continue treatment. Section 9.1 For methotrexate, sulfasalazine and leflunomide Regulation 46 (2) of SI 2004/1031 will now apply so sites are only required to apply a dispensing label not the OCTRU non-trial stock label. Section 10.4 'Reporting procedures for Serious Adverse Events', clarification provided on recipient of SAE forms. Section 10.7 'Reporting procedure for pregnancy', information added. Section 10.8, Reporting obligations to AbbVie are listed following receipt of an SAE form and pregnancy notification form Section 10.11, Product complaints section updated for clarification on procedure Section 12.3, added information about patient datasets. Section 21.0, changes made to 'APPENDIX D: SAE Reporting flow chart'.

10	V10.0		L.Coates I.Marian S.Dutton Y.Sinomati	New DSMC chair added. Synopsis 2, section 5, 8.5, 8.6 and 11.1 the primary and secondary sections have been clarified. The primary outcome is PASDAS score as a continuous outcome measure. PASDAS score (on a continuous scale) at 48 weeks post randomization was added to the secondary outcome measures. The planned sample size has changed to 192 from 315. Follow up duration has changed. Deleted original 315 sample size. Treatment duration has been changed to 36-48 weeks. Planned end date changed to Oct 2023. Section 4 – Background on the rationale for the updated sample size of 192. Trial design, section 6 and 8.6, updated; within the last 24 weeks of recruitment patients will only have visit assessments conducted up to week 36 and then will revert to the MONITOR cohort. IMP will be provided until week 32. Total of new sample size (192) and 64 in each arm. Section 9.6 Added treatment arm3. Statistics section 11.1 first section updated to only include information on the primary outcome. The secondary outcome table and text has been moved lower down in this section. Section 11.3 updated to include the change to the way the new primary outcome is specified. Ultrasound scan in arm 3 patients removed from section 4, 5, 8.6, 11.1 and Appendix C table. This is due to the decrease in sample size and it is not required. Section 11.2, Some participants will not progress to week 48 data if recruited towards the end of the recruitment period, however this data can be collected as part of the MONITOR cohort. Adverse events removed from baseline section in Appendix C.

				Footnote added below Appendix C table to state SPEED patients will complete assessments up to week 36 and then revert to the MONITOR cohort. Following recent publication on PASDAS score being used as a continuous outcome by Michelle L M Mulder (2020) (reference number 43 added in references section), Referred to in section 11.3. following information provided by this publication the primary outcome has been changed to continuous outcome. MONITOR Protocol publication added to the References section.
11	V11.0	24Jan2023	Yvonne Sinomati	Planned end date changed to October 2024. Key trial contacts telephone number for Dr Laura Coates removed, telephone number added for study team. Name change for our new statistician and address added for the Botnar. AbbVie added as a funder. NIHR funding changed to 'was originally funded by NIHR'. Subsequent additional funding from Janssen-Cilag Ltd, UCB Biopharma SRL added to funder sections. Secondary and primary outcomes in section 5, sections 11.1, 11.3 and the history of changes amendment 10 section have been updated for consistency with the Synopsis to clarify the PASDAS score (on a continuous scale) is being used. The secondary objective and its outcome measure have been changed for consistency in section 5. Typographical corrections.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC or MHRA.