Trial Title: Clinical effectiveness of symptomatic therapy compared to standard step up care for the treatment of low impact psoriatic oligoarthritis: a 2 arm parallel group feasibility study

/ Short title: POISE - Psoriatic Oligoarthritis Intervention with Symptomatic thErapy

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Chief Investigator:	Dr Laura Coates Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford
Principal Investigators:	Dr William Tillett, Royal United Hospital, Bath, UK Dr Deepak Jadon, University of Cambridge Hospitals NHSFT, Cambridge, UK Dr Nicola Gullick, Rheumatology, University Hospital, Clifford Bridge Road, Coventry, UK Ben Thompson, Newcastle, The Newcastle upon Tyne Hospitals NHS Foundation Trust , Freeman Hospital, Newcastle upon Tyne , UK
Sponsor:	University of Oxford Clinical Trials and Research Governance, Boundary Brook House, Churchill Drive, Headington, OXON, OX3 7LQ Email: ctrg@admin.ox.ac.uk
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Chief Investigator Signature:

Statistician Signature:

Please declare any/no potential conflicts of interest.

Laura Coates – none

William Tillett – none

Deepak Jadon – none

Nicola Gullick - none

Ben Thompson - none

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

Chief Investigator	Dr Laura Coates Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford Botnar Research Centre, Windmill Road, Oxford, OX3 7LD Tel 01865 737838 Laura.coates@ndorms.ox.ac.uk
Sponsor	Ms Heather House Boundary Brook House, Churchill Drive, Headington, OXON, OX3 7LQ Email: ctrg@admin.ox.ac.uk
Trial Management Office	Monitor PsA Study, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, Windmill Road, Oxford, UK, OX3 7LD. Email: monitorpsa@ndorms.ox.ac.uk
Clinical Trials Unit	OCTRU Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, Windmill Road, Oxford, UK, OX3 7LD. Tel: 01865 223469 ; Email: octrutrialshub@ndorms.ox.ac.uk
Statistician(s)	Ines Rombach, Medical Statistician Susan Dutton, Medical Statistician OCTRU/Center for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford Botnar Research Centre, Windmill Road, Oxford, OX3 7LD Ines.rombach@ndorms.ox.ac.uk Susan.dutton@ndorms.ox.ac.uk
Trial Steering Committee	Chair – Dr Philip Helliwell, Research Rheumatologist, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, email:p.helliwell@leeds.ac.uk
Data Safety and Monitoring Committee	Chair – Dr Jon Packham, Consultant Rheumatologist, Staffordshire and Stoke on Trent Partnership NHS Trust, Stoke on Trent. Jon.Packham@ssotp.nhs.uk

2. SYNOPSIS

Trial Title	Clinical effectiveness of symptomatic therapy compared to standard step up care for the treatment of low impact psoriatic oligoarthritis:a 2 arm parallel group feasibility study.	
Short title	POISE - Psoriatic Oligoarthritis Intervention with Symptomatic thErapy	
Trial Design	Feasibility study within Trials Within Cohorts (TWiCs) design	
Trial Participants	Participants from the MONITOR-PsA cohort with mild psoriatic arthritis	
Planned Sample Size	60, 30 to the cohort as controls and 30 receiving the intervention	
Sites	1) Nuffield Orthopaedic Centre, Windmill Rd, Headington, Oxford OX3 7HE. Tel: 0300 304 7777 2) Royal National Hospital for Rheumatic Diseases, Upper Borough Walls, Bath, BA1 1RL. Tel: 01225 465941 3) Addenbrooke's Hospital, Hills Rd, Cambridge CB2 0QQ. Tel: 01223 245151 4) Coventry Rheumatology, University Hospital, Clifford Bridge Road, Coventry CV2 2DX, Tel: 024 7696 6705 5) Newcastle, The Newcastle upon Tyne Hospitals NHS Foundation Trust , Freeman Hospital, Newcastle upon Tyne, NE7 7DN. Tel: 0191 233 6161	
Treatment duration	48 weeks	
Follow up duration	48 weeks	
Planned Trial Period	16th July 2018 to 16th July 2021	
	Objectives	Outcome Measures
Primary	To determine the feasibility of conducting a future definitive trial to establish whether a subgroup of Participants with mild psoriatic arthritis (PsA) can be safely and effectively managed without disease-modifying anti-rheumatic drugs (DMARDs).	To establish the acceptability of conservative management in mild PsA and the feasibility of a future definitive trial the study will assess 1. The proportion of eligible Participants in the cohort over the recruitment period for POISE 2. The proportion of Participants consenting to the study which will indicate that they find the intervention acceptable 3. The proportion of Participants not offered DMARD therapy during the 48 week trial period (DMARD therapy will be offered if Participants have active disease despite 2 doses of glucocorticoids to the same

		joint within a 6 month period as stated in section 4)
Secondary	To develop the design of a future definitive trial to establish whether a subgroup of Participants with mild PsA can be safely and effectively managed without DMARDs.	The primary outcome of the future study will be the proportion of Participants achieving a good response level (reduction from baseline of >1.6 and final score of <3.2) in the PsA Disease Activity Score (PASDAS)[2]. Descriptive data on PASDAS will be collected to allow accurate sample size estimations for any future trial.
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 They may be required in later studies on the cohort as part of the TWiCs approach. ACR20, 50 and 70[23]	• Safety (AEs, ADRs and SAEs reported during the trial period) • Treatment satisfaction measured by the treatment satisfaction questionnaire for medication (TSQM)[26] • The feasibility of conducting an economic evaluation of the delayed DMARD therapy group will be assessed. An assessment will be made on the best way to express cost-effectiveness and most appropriate sources of unit cost data for potential resource consequences.
Investigational Medicinal Products with Formulation, Dose, Route of Administration	Glucocorticoids: • Methylprednisolone acetate BP 10-40mg to be given as intra-articular injection or 80-120mg to be given as intra-muscular injection as detailed in section 9.1 • Triamcinolone 10-40mg to be given as intra-articular injection or 80-120mg to be given as intra-muscular injection as detailed in section 9.1	

3. ABBREVIATIONS

ACPA	Anti citrullinated peptide antibody
ACR	American College of Rheumatology
ADR	Adverse Drug Reaction (i.e. ARs and SARS)
AE	Adverse event
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AR	Adverse reaction
BASDAI	Bath ankylosing spondylitis disease activity index

BASFI	The Bath Ankylosing Spondylitis Functional Index
BASMI	Bath ankylosing spondylitis metrology index
BSA	Body surface area
CASPAR	ClASsification criteria for Psoriatic Arthritis
CI	Chief Investigator
CRF/eCRF	Case Report Form/electronic Case Report Form
CRP	C-reactive protein
CTRG	Clinical Trials and Research Governance
DMARD	Disease-modifying anti-rheumatic drugs
DMSC	Data Monitoring and Safety Committee
DSUR	Development Safety Update Report
eGRF	estimated glomerular filtration rate test
EMS	Early Morning Stiffness
EULAR	European League Against Rheumatism
EuroQol	European Quality of Life
GCP	Good Clinical Practice
GP	General Practitioner
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HAQ	Health Assessment Questionnaire
HRQol	Health-related quality of life
HRA	Health Research Authority
ICF	Informed Consent Form
IL12/23/17	Interleukin
IMP	Investigational Medicinal Product
LEF	Leflunomide
MHRA	Medicines and Healthcare products Regulatory Agency
NSAID	Non-steroidal anti-inflammatory drugs
NHS	National Health Service
NRES	National Research Ethics 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
PsA	Psoriatic Arthritis
PROMS	Patient Reported Outcome Measures
PSAID	Psoriatic Arthritis Impact of Disease
RCT	Randomised Controlled Trial
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RF	Rheumatoid factor
RNHRD	Royal National Hospital for Rheumatic Diseases
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SJC	Swollen joint count
SmPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SPARCC	Spondyloarthritis Research Consortium of Canada
SSZ	Sulfasalazine
SUSAR	Suspected Unexpected Serious Adverse Reactions
TJC	Tender joint count
TSC	Trial Steering Committee
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
US	Ultrasound
VAS	Visual Analogue Scale
WBC	White Blood Count
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 PsA. Two-thirds of people with PsA suffer progressive joint damage with associated disability[5, 6]. People with PsA have similar functional and quality of life impairment to rheumatoid arthritis[7]. PsA is associated with a reduced life expectancy[8] related to the 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].

PsA is a highly heterogenous disease[11] with a proportion of patients having mild non-progressive disease[12]. Well validated prognostic factors in PsA can identify these patients including number of active joints, systemic inflammation levels, radiographic damage and functional ability at presentation[13-15]. There is little research addressing outcomes and treatment options for mild disease[16-18]. It is likely that some patients are over treated with conventional 'step up' therapy leading to unnecessary side effects for the patient and costs to the healthcare system. A previous study in undifferentiated peripheral spondyloarthritis found that 55% of Participants did not require disease-modifying anti-rheumatic drugs (DMARDs) and could be managed with only intra-articular steroid injections and analgesia. However, only 4 of 59 Participants had a diagnosis of PsA [16]. In established disease ultrasound (US) inflammation in the joints predicts future flare of disease in those already on treatment[19].

This trial will investigate the feasibility and acceptability of the study design to establish whether Participants with mild PsA can be managed without DMARDs. Participants with newly diagnosed PsA will be eligible if they fulfil the following criteria:

1. Oligoarthritis (<5 joints involved)
2. No poor prognostic markers

Baseline US may identify a sub-group of Participants for whom conservative treatment is most beneficial. This data will enable me to design and power a definitive trial of delayed DMARD treatment for mild PsA.

The intervention will delay standard treatment with disease-modifying anti-rheumatic drugs (DMARDs) and use local steroid injections to affected joints instead. Oral non-steroidal anti-inflammatory drugs (NSAIDs) will also be allowed as concomitant medication as indicated for individuals. Local steroid injections will include injections with methylprednisolone or triamcinolone.

Potential risks include side effects from NSAIDs, side effects from steroid administration or side effects from the intra-articular administration. All of these will be detailed in the patient information sheet. In case of requirement of more than 2 local injections to any specific joint within a 6 month timeframe, Participants will be withdrawn from the treatment protocol and be treated as per usual care (in most cases with disease-modifying anti-rheumatic drugs (DMARD) therapy). This is to ensure that risks in delaying treatment are mitigated.

This trial is nested within a cohort (MONITOR-PsA) forming the basis of a Trials Within Cohorts (TWiCs) design. This method recruits a central cohort having "treatment as usual" with regular observations and then adds pragmatic trials of alternative therapies where a random group of eligible Participants are selected. This allows robust generalizability from studies to routine health care, avoids attrition and disappointment bias from controls in open label studies as Participants only receive information relevant to their care, aids recruitment to trials, allows routine collection of long term outcomes and increases

efficiency with multiple trials within one cohort[20]. This will allow us to address outcomes with a pragmatic 'treat to target' approach in a real-life cohort and compare other therapeutic interventions. This design is particularly suited to open label trials with "treatment as usual" as the comparator. It is ideal for chronic conditions, situations where multiple trials may be performed and where expensive desirable treatments are being trialed[20]. Thus Participants in this POISE study will be recruited from and followed as part of the MONITOR cohort.

4.1. Proposed interventions

A schema of the proposed interventions is shown in appendix B.

All Participants will be randomized into either arm 1 or 2 of the POISE trial and those randomized to the offer of an intervention will also be asked to have a baseline ultrasound (US) scan of key joints and entheses to establish the degree of any subclinical inflammation. Baseline ultrasound scoring of disease activity is included as an exploratory outcome. A baseline ultrasound of 44 joints and 10 entheses will be performed as the optimal sites for US in PsA are not yet established. This allows calculation of the PsA sonographic (PsASon) scoring system[21].

ARM 1: Control 'step-up' therapy in cohort (MONITOR-PsA Cohort study REC REF 17/SC/0556). Therapy for the cohort is defined by standard NHS practice in these PsA clinics following current international recommendations[22] and National requirements for the prescription of biologic therapy[4, 23-25]. 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 (SSZ) or leflunomide (LEF)) added or switched to at the discretion of the rheumatologist. In cases of failure of two disease-modifying anti-rheumatic drugs (DMARDs), treatment can be escalated to biologic therapy as per National Institute for Health and Clinical Excellence (NICE) recommendations[4, 23-25] usually with a tumour necrosis factor (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 Cohort protocol.

ARM 2: Symptomatic therapy arm. The intervention will delay standard treatment with disease-modifying anti-rheumatic drugs (DMARDs) and use local glucocorticoid injections to affected joints instead. Oral non-steroidal anti-inflammatory drugs (NSAIDs) will also be allowed as concomitant medication as indicated for individuals. Local glucocorticoid injections will include injections with methylprednisolone or triamcinolone. Participants will be reviewed at weeks 12, 24, 36 and 48 routinely. They will also have a trial helpline contact so that if their disease flares between these visits they can contact the team to be reviewed at an extra visit in between these. All active joints will be treated with glucocorticoid injections. Glucocorticoid injections can be either be given as an intra-articular injection to an inflamed joint or as an intra-muscular injection if multiple joints are involved. The choice of glucocorticoid will be left to the treating physician depending on the joint involved and local routine practice. If any joint requires more than 2 local injections of glucocorticoid within a 6 month period, then the patient is deemed to have failed symptomatic therapy and will be withdrawn from the treatment protocol and be treated as per usual care (in most cases with DMARD therapy). If Participants require DMARD therapy, they will be offered rescue therapy as per usual clinical care but will be asked to continue with data collection for the trial. This is to ensure that sufficient data is collected for the trial but risks in delaying treatment to the individual are mitigated.

Methylprednisolone acetate BP (such as Depo-Medrone®)
This will be supplied as a sterile aqueous suspension in vials containing 40 mg methylprednisolone acetate, macrogol, sodium chloride, myristyl-gamma-picolinium chloride and sterile water for injections.

This drug will be used for local injections given as intra-articular injections to inflamed joints or local injections to active enthesitis around tendon insertions. In the case of multiple active joints, an intramuscular injection of methylprednisolone acetate can be used instead of intra-articular injections. Each vial of methylprednisolone acetate will be used as supplied. Doses of between 10 and 120mg of methylprednisolone will be used according to the table below:

Joint	Dose
Small joint/enthesis e.g. fingers	10-20 mg
Medium joint/enthesis e.g. wrist	20-40 mg
Large joint e.g. knee	40-80 mg
Intramuscular injection	80-120 mg

Details of how these will be used are given further in section 4.1 on interventions.

Triamcinolone (such as Kenalog®)
This will be supplied as a sterile aqueous suspension in vials containing 40mg triamcinolone, benzyl alcohol, polysorbate 80m sodium carboxymethylcellulose, sodium chloride and sterile water for injections.

This drug will be used for local injections given as intra-articular injections to inflamed joints or local injections to active enthesitis around tendon insertions. In the case of multiple active joints, an intramuscular injection of triamcinolone can be used instead of intra-articular injections. Each vial of triamcinolone will be used as supplied. Doses of between 10 and 80mg of triamcinolone will be used according to the table below:

Joint	Dose
Small joint/enthesis e.g. fingers	10-20 mg
Medium joint/enthesis e.g. wrist	20-40 mg
Large joint e.g. knee	40 mg
Intramuscular injection	80-120 mg

Details of how these will be used are given further in section 4.1 on interventions.

5. OBJECTIVES AND OUTCOME MEASURES

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objective To determine the feasibility of conducting of a future definitive trial to establish whether a subgroup of Participants with mild PsA can	To establish the acceptability of conservative management in mild PsA and the feasibility of a future definitive trial the study will assess	1 & 2: Baseline assessment in MONITOR-PsA cohort 3: follow-up at 48 weeks

be safely and effectively managed without DMARDs.	1. The proportion of eligible Participants in the cohort over the recruitment period for POISE 2. The proportion of Participants consenting to the study which will indicate that they find the intervention acceptable 3. the proportion of Participants not offered DMARD therapy during the 48 week trial period (DMARD therapy will be offered if Participants have active disease despite 2 doses of glucocorticoids to the same joint within a 6 month period, as in section	
Secondary Objectives To develop the design of a future definitive trial to establish whether a subgroup of Participants with mild PsA can be safely and effectively managed without DMARDs.	The primary outcome of the future study will be the proportion of Participants achieving a good response level (reduction from baseline of ≥1.6 and final score of ≤3.2[1]) in the PsA Disease Activity Score (PASDAS)[2]. Descriptive data on PASDAS will be collected to allow accurate sample size estimations for any future trial. Baseline US assessment will be related to future requirement of DMARD therapy to consider if baseline US should be stratified for in the randomisation of a future trial.	All follow-up visits where measured - as detailed in Appendix C schedule of procedures. US of joints and entheses at baseline
Exploratory objectives To evaluate exploratory outcome measures that may be used to generate hypotheses for future studies. They may be required in later	• ACR20, 50 and 70[23] • Safety (AEs, ADRs and SAEs reported during the trial period) • Treatment satisfaction measured by the treatment	All follow-up visits where measured - as detailed in Appendix C schedule of procedures.

studies on the cohort as part of the TWiCs approach	satisfaction questionnaire for medication (TSQM)[26] The feasibility of conducting an economic evaluation of the delayed DMARD therapy group will be assessed. An assessment will be made on the best way to express cost-effectiveness and most appropriate sources of unit cost data for potential resource consequences.	

6. TRIAL DESIGN

A flowchart of the study is shown in Appendix A.

This is a randomised open-label feasibility trial assessing the acceptability of conservative management in mild PsA and the feasibility of a future definitive trial within a cohort in a "Trials within Cohorts" or TWiCs design. A maximum of 60 Participants will be recruited (30 to the cohort, arm 1 as controls and 30, arm 2 receiving the intervention). The number is an estimate, as at present we do not know how many Participants with mild disease will be eligible and willing to participate. It is estimated that around 15% of Participants referred with new PsA may be eligible. Each participant will be followed for 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 48. Participants in the intervention arm will also be able to attend for joint injections as required in between these visits via a trial helpline. At all visits, Participants will be assessed clinically for disease activity and will be asked to complete patient reported outcomes via questionnaires.

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 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 adult 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 mild disease defined as low disease activity and impact will be eligible (see below).

7.2. Inclusion Criteria

- Participants consented to the PsA inception cohort (MONITOR-PsA) and to be approached for alternate interventional therapies.
- Participants with mild disease as defined by:
- Oligoarticular disease with <5 active joints at baseline assessment.Participant is willing and able to give informed consent for participation in the trial.
- Male or female.
- Aged 18 years or above.

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 (defined as true abstinence, oral contraceptives, implants, intrauterine device, barrier method with spermicide, or surgical sterilization) 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 6 weeks of enrolment:
    - Haemoglobin count > 8.5 g/dL
    - White blood count (WBC) > 3.5 x 10^9/L
    - Absolute neutrophil count (ANC) > 1.5 x 10^9/L
    - Platelet count > 100 x 10^9/L
    - ALT and alkaline phosphatase levels <3 x upper limit of normal
    - eGFR

- 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:

- ≥1 poor prognostic factors for psoriatic arthritis, from
    - raised C reactive protein (CRP) defined as > 4g/dl for standard non-hsCRP
    - radiographic damage defined as the presence of ≥ 1 erosion on plain radiographs of the hands and feet
    - health assessment questionnaire (HAQ) score > 1
- Contraindications to non-steroidal anti-inflammatory drugs
- Previous treatment for articular disease with synthetic DMARDs (including methotrexate, leflunomide or sulfasalazine) or biologic DMARDs (including TNF, IL12/23 or IL17 inhibitor therapies) or targeted synthetic DMARDs (PDE4 of JAK inhibitor therapies).

- Female patient who is pregnant, breast feeding or planning pregnancy during the course of the trial.
- Significant renal or hepatic impairment.
- Scheduled elective surgery or other procedures requiring general anaesthesia during the trial.
- Any other significant disease or disorder which, in the opinion of the Investigator, may either put the patients at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial.
- Patients who have participated in another research trial involving an investigational product in the past 12 weeks.

8. TRIAL PROCEDURES

A flowchart for recruitment and inclusion in this TWiCs cohort is shown in appendix B.

8.1. Screening and Eligibility Assessment

Potential Participants will be identified from the MONITOR-PsA cohort which is recruited from new referrals to the rheumatology service particularly those referred to the early arthritis clinic. Participants will be identified and approached initially by their reviewing/treating clinical care team and will be given brief information about the cohort. If they are interested, a Participant Information Sheet and consent form 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 Participants will be asked to consent to the following items as part of the Trials Within Cohorts 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.

8.2. Recruitment

If Participants are randomised to be offered the intervention then they will be approached initially by their reviewing/treating clinical care team within the cohort study and will be given brief information about the

intervention. If they are interested they will be given the full patient information sheet (PIS) and informed consent form (ICF) for this trial as well as a verbal explanation of the trial. They will be allowed as much time as they wish to consider their participation as stated in 8.3. If they decline to consent then they will be followed only in the cohort (in line with their previous cohort consent). If they are happy to consent to the intervention, then they will be asked to sign the consent form prior to any study related procedures occurring.

8.3. Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form 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 Participants and one will be retained in the healthcare record. The original will be retained at the sites.

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 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
- Duration of disease prior to diagnosis (<12 months, ≥12 months)

The randomisation schedule will be designed by the statistician from OCTRU and will be held within the database system.

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

A member of the research team will undertake disease activity assessments blinded.

8.5. Baseline Assessments

Baseline assessments must be performed before Participants start on treatment. The intervention will delay standard treatment with DMARDS and use local glucocorticoid injections to affected joints if and when required. See Appendix C 'Schedule of procedures' for the time points of when the corticosteroids are dispensed. The following will be assessed for all Participants within the cohort study (MONITOR-PsA) 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, WBC, platelet count, neutrophils, ALT.
- Antibody markers: anti-citrullinated peptide antibodies (ACPA) and rheumatoid factor (RF)
- *Efficacy bloods: CRP and eGFR
- PsA history: PsA type; symptom onset; diagnosis date; peripheral and axial early morning stiffness (EMS); inflammatory axial pain.
- Classification Criteria for Psoriatic Arthritis (CASPAR) Criteria:
    - Evidence of current psoriasis
    - Personal history of psoriasis
    - Family history of psoriasis nail dystrophy including onycholysis, pitting, and hyperkeratosis
    - Evidence of current or documented history of dactylitis
    - Personal history or 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[27] and Spondyloarthritis Research Consortium of Canada (SPARCC)[28] 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].

Specific to this study protocol, patients will be randomized into either arm 1 or 2 of the POISE trial and those randomized to the offer of an intervention will also be asked to have a baseline ultrasound (US) scan of key joints and entheses to establish the degree of any subclinical inflammation. Baseline ultrasound scoring of disease activity is included as an exploratory outcome. A baseline ultrasound of 44 joints and 10 entheses will be performed as the optimal sites for US in PsA are not yet established. This allows calculation of the PsA sonographic (PsASon) scoring system[21].

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

- *Global disease activity visual analogue scale (VAS)
- Patient pain VAS
- Health assessment questionnaire (HAQ)[31]
- PsA impact of disease (PSAID)[32]
- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- *SF36[33]
- EQ-5D-5L[34]
- Work productivity and activity impairment (WPAI)[35]
- BASFI

The primary outcome of a future proposed trial would be the proportion of Participants maintaining low disease activity as measured by the PASDAS (≤3.2) at week 48. The PASDAS is a composite score including both clinical assessment and patient reported outcomes. It is calculated as (((0.18√physician global VAS) + (0.159√patient global VAS) – (0.253 x √SF36-PCS) + (0.101 x LN (SJC+1)) + (0.048 x LN (TJC+1)) + (0.23 x LN (Leeds enthesitis index +1)) + (0.37 LN (tender dactylitis count+1)) + (0.102 x LN (CRP+1)) +2) x 1.5. The items in the PASDAS are marked above in the list of outcomes with an asterisk. Descriptive data on the PASDAS will be collected in this feasibility study to allow for estimation of appropriate sample size for a future definitive trial.

8.6. Subsequent Visits

Follow up will be for 48 weeks with data to be collected at 12, 24, 36 and 48 weeks for this trial. Local glucocorticoid injections will include injections with methylprednisolone or triamcinolone. See Appendix C 'Schedule of procedures' for the time points of when the corticosteroids are dispensed in the case of active arthritis requiring treatment. Participants receiving the intervention will also be able to contact the trials team via a helpline if they require steroid injections in between these visits. All active joints will be treated with glucocorticoid injections which are either given as an intra-articular to an inflamed joint or as an intra-muscular injection if multiple joints are involved.

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: haemoglobin, WBC, platelet count, neutrophils, ALT.
- Efficacy bloods: CRP and eGFR
- 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[27] and (SPARCC)[28] enthesitis index
    - (PASI) (BSA)

- Physician's VAS of overall disease activity

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

- Global disease activity visual analogue scale (VAS)
- Patient pain VAS
- Health assessment questionnaire (HAQ)[31]
- PsA impact of disease (PSAID)[32]
- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- SF36[33]
- Work productivity and activity impairment (WPAI)[35]
- Health system utilisation data
- Treatment satisfaction measured by the treatment satisfaction questionnaire for medication (TSQM)[26]
- BASFI
- Compliance with treatment

At certain visits additional assessments will be performed:

- Week 24 and 48
  - EQ-5D-5L[34]
  - 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].

<u>At baseline and 48 weeks</u>

- (BASMI) (only if clinical/imaging evidence of axial involvement)

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. The results of the routine NHS blood tests will be recorded to monitor safety of the treatment and calculate composite measures of efficacy. Any unusual values will be reported as AEs/SAEs where appropriate and values of CRP will be recorded at each visit to allow calculation of composite measures of efficacy

8.8. Discontinuation/Withdrawal of Participants from Trial Treatment

Each participant has the right to withdraw from the trial at any time, with data collected up to the point of withdrawal will be 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 the trial treatment 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
- Requirement of more than 2 local intra-articular injections of steroid to a single joint within a 24 week time period

If the participant withdraws from active treatment in the study, 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.

If Participants require DMARD therapy, they will be offered rescue therapy as per usual clinical care but will be asked to continue with data collection for the trial. Withdrawn Participants will not be replaced. The reason for withdrawal 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/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.

8.10. Definition of End of Trial

The end of study is when all participant visits are complete and all data has been entered and queries closed.

9. INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

9.1. IMP Description

Methylprednisolone Acetate and Triamcinolone are NHS supply and will be provided by the NHS pharmacy. Pharmacy will be responsible for labelling the IMPs in accordance with the requirements of the Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994.

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.

OCTRU will provide labels for all IMPs (non-trial stock) for use in accordance with the requirements of the Medicines for Human Use (Clinical Trials) Regulations 2004 (and amended in 2006). The pharmacy at each NHS site will be responsible for applying the labels the drug in accordance with the above legislation.

Methylprednisolone acetate BP

This will be supplied as a sterile aqueous suspension in vials containing 40 mg methylprednisolone acetate, macrogol, sodium chloride, myristyl-gamma-picolinium chloride and sterile water for injections.

This drug will be used for local injections given as intra-articular injections to inflamed joints or local injections to active enthesitis around tendon insertions. In the case of multiple active joints, an intramuscular injection of methylprednisolone acetate can be used instead of intra-articular injections. Each vial of methylprednisolone acetate will be used as supplied. Doses of between 10 and 120mg of methylprednisolone will be used according to the table below:

Joint	Dose
Small joint/enthesis e.g. fingers	10-20 mg
Medium joint/enthesis e.g. wrist	20-40 mg
Large joint e.g. knee	40-80 mg
Intramuscular injection	80-120 mg

Details of how these will be used are given further in section 4.1 on interventions.

Triamcinolone

This will be supplied as a sterile aqueous suspension in vials containing 40mg triamcinolone, benzyl alcohol, polysorbate 80m sodium carboxymethylcellulose, sodium chloride and sterile water for injections.

This drug will be used for local injections given as intra-articular injections to inflamed joints or local injections to active enthesitis around tendon insertions. In the case of multiple active joints, an intramuscular injection of triamcinolone can be used instead of intra-articular injections. Each vial of triamcinolone will be used as supplied. Doses of between 10 and 80mg of triamcinolone will be used according to the table below:

Joint	Dose
Small joint/enthesis e.g. fingers	10-20 mg
Medium joint/enthesis e.g. wrist	20-40 mg
Large joint eg knee	40 mg
Intramuscular injection	80-120 mg

Details of how these will be used are given further in section 4.1 on interventions.

9.2. Storage of IMP

Vials of methylprednisolone acetate and triamcinolone will be stored at room temperature and do not need to be protected from light.

9.3. Compliance with Trial Treatment

The methylprednisolone acetate or triamcinolone will be given by one of the study doctors or nurses in the form of an intra-articular or intra-muscular injection. The dose of glucocorticoid actually given will be recorded.

9.4. Accountability of the Trial Treatment

Methylprednisolone and Triamcinolone supplied and used for the trial will be recorded in the trial eCRF.

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 any DMARD therapy supplied as rescue therapy within the trial. Participants will be aware of their treatments as this trial is open label as will their general practitioner. 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 an IMP in the study (e.g. NSAIDs or steroid injections) will be eligible to continue with these as standard NHS supply.

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:

Related: The adverse event follows a reasonable temporal sequence from trial medication administration. It cannot reasonably be attributed to any other cause.

Not Related: The adverse event is probably produced by the participant's clinical state or by other modes of therapy administered to the participant.

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:

- Participant 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.

All SAEs must be reported on the SAE reporting form to OCTRU and the study team 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 the Medical Monitor. It will also be reviewed in the safety report at the next meeting of the Data Safety and Monitoring Committee. All SAE information must be recorded on an SAE form and faxed, or scanned and emailed, to OCTRU. Additional and further requested information (follow-up or corrections to the original case) will be detailed on a new SAE Report Form and faxed/emailed to OCTRU. Any SAEs that are considered related to drug and unexpected (i.e. suspected unexpected serious adverse reactions or SUSARs) will also be reported to the sponsor (the Clinical Trials and Research Governance or CTRG at the University of Oxford).

10.5. Expectedness

The SAE form will be reviewed by the CI, who together with the trial management team in the OCTRU office will make an independent assessment of causality and will perform an assessment of expectedness, determined according to the Summary of Product Characteristics. Additional and further requested information (follow-up or corrections to the original case) will be detailed on a new SAE Report Form and faxed or scanned and emailed to the trial office.

10.6. SUSAR Reporting

All SUSARs will be reported by OCTRU on behalf of the CI to the MHRA 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 will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current trial.

10.7. 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, RES, HRA (where required)and Sponsor.

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

Specific feasibility analyses include the calculation of the proportions of:

- eligible Participants in the cohort over the recruitment period for POISE
- eligible Participants consenting into the POISE trial
- Participants requiring escalation to DMARD therapy within the first 48 weeks.

If feasibility of such a trial is confirmed based on the assessments above, then the other data collected within the study will be used to plan and design a future RCT. This would be an independent study that would not reuse data from these participants. However the data from this feasibility study will allow us to examine the descriptive statistics around the different outcome measures to allow development of a sample size and to plan which outcomes would be chosen as primary and secondary key outcomes. To aid design of a future RCT, analysis will focus on descriptive statistics and confidence interval estimation rather than formal hypothesis testing as this is not a powered study. Descriptive statistics will be produced by trial arm for baseline data assessing PsA phenotype and disease activity. Outcome measures, including PASDAS and PSAID, will be summarized at the different follow-up time points. Estimates of the differences in outcomes between the groups and corresponding 95% confidence intervals will be presented for the 48 weeks follow-up time point. Estimates of the PASDAS outcomes at 48 weeks will be used to power any future definitive trial. Reported tolerance, particularly those side effects related to treatments will be presented for both groups

Reasons for non-consent and any suggestions for improving the study design as well as the feasibility of outcomes will be considered when designing any future definitive trial.

11.2. Health Economics analysis

The economic evaluation will estimate the cost effectiveness of the proportion of Participants not offered DMARD therapy during the 48 week trial period in adults with mild non-progressive disease. Primary, Community and Social care service use will be collected at 24 weeks and 48 weeks post randomisation using patient self-reported questionnaires. The 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 British National Formulary 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 comparison 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 descriptive only given the sample size in this

feasibility study and presented in terms of expected Incremental Cost Effectiveness Ratios (ICERs); ΔCosts/ ΔQALY , where , ΔCosts is the difference in total costs between the interventions and ΔQALY is the difference in utility between interventions),The Number of Participants

As a feasibility study, one of our key outcomes is the recruitment rate itself. Publications suggest a sample size of 12-30 patients per arm for a feasibility study [36, 37] and therefore a maximum of 60 Participants will be randomised in this study in a 1:1 ratio.

11.3. The Level of Statistical Significance

To aid design of a future RCT, analysis will focus on descriptive statistics and confidence interval estimation rather than formal hypothesis testing.

11.4. 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. 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.

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

Missing data will be reported but not taken into account when presenting descriptive statistics. Any pattern to missing data (suggesting that certain outcomes are not recorded well) will be investigated to inform a future trial design.

11.6. Inclusion in Analysis

The intention to treat population will include those who have been offered the treatment intervention or those randomised to stay in the cohort as controls, regardless of whether they accepted the offered treatment or received the intervention. Participants will be analysed based on their randomised groups. Numbers of Participants who actually received the intervention will also be summarised as this will provide additional information to power the future definitive study.

Information on eligibility and willingness to consent to the feasibility study will be taken from the MONITOR PsA cohort study.

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

A detailed statistical analysis plan will be drawn up prior to participant 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 final 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

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.

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 according to the 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.

Oxford, Coventry and Newcastle: Participants will complete their PROMs on a tablet computer using a software developed by the OCTRU. This will securely store the data on a secure server within a university of Oxford facility at the John Radcliffe Hospital alongside data entered by the healthcare team. Participant 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.

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. Participant 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. 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 participant 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.

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 will be drawn up which will fully explain all aspects of data management.

13. ORGANISATION

13.1. Project timetable and milestones

The aim is to recruit a maximum of 60 Participants to the trial over a period of 30 months.

13.2. Trial Steering Committee

The Trial Steering Committee (TSC) provides overall supervision of the cohort and the trial on the behalf of the funder and is chaired by an Independent Member. The TSC abides by the OCTRU Standard Operating Procedure and the OCTRU TSC Charter which is based on the MRC Clinical Trials Unit template. The TSC will monitor study progress and conduct and advise on scientific credibility. Meetings of the TSC will take place at least once a year during the participant recruitment period.

13.3. Trial Management Group

The Trial Management Group (TMG) is made up of the Investigators listed on the front of this protocol, and staff working on the project within OCTRU and NDORMS. This group will oversee the day-to-day running of the trial and will meet regularly.

13.4. 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 Trial Steering Committee 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.

13.5. Local Co-ordination

Each participating site will identify a local PI and local research clinician (as necessary). The responsibility of local research clinicians will be to:

1. Be familiar with the trial
2. Liaise with the coordinating team in Oxford
3. Disseminate MONITOR PsA and POISE protocols and information to staff involved in the trial locally
4. Ensure mechanisms are in place to facilitate the recruitment of eligible Participants, monitor recruitment locally and identify barriers to recruitment and work towards solving them
5. Ensure timely consenting of Participants
6. Work with local Research and Development staff to facilitate approvals
7. Deal promptly with missing data queries and return these to the study office
8. Facilitate other aspects of local collaboration as appropriate
9. Make all data available for verification, audit and inspection purposes as necessary
10. Ensure participant confidentiality is respected by all persons at all times
11. The PI at each site will identify local staff who will be responsible for delegated duties. The Delegation Log should be updated accordingly. New staff should be trained and added to the log as the study progresses. When the Delegation Log is updated, a copy should be sent to the study coordinating office in Oxford. The Delegation Log is part of the working file and must be updated when any responsibilities are delegated locally. A copy of the updated version of the log must be sent to the study office.

14. QUALITY ASSURANCE PROCEDURES

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and SOPs.

Regular monitoring will be performed according to GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the team within OCTRU will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. A Monitoring Plan will be developed according to OCTRU's SOPS which involves a risk assessment. The monitoring activities are based on the outcome of the risk assessment and may involve central monitoring and site monitoring.

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. Details of the DSMC are found in section 13.4.

15. 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 Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, MHRA and the NHS host organisation within seven calendar days.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

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

16.2. Guidelines for Good Clinical Practice

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

16.3. 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.

16.4. 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.

16.5. 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 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.

16.6. 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.

16.7. Other Ethical Considerations

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

17. FINANCE AND INSURANCE

17.1. Funding

This study is 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.

17.2. 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.

18. 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.

19. REFERENCES

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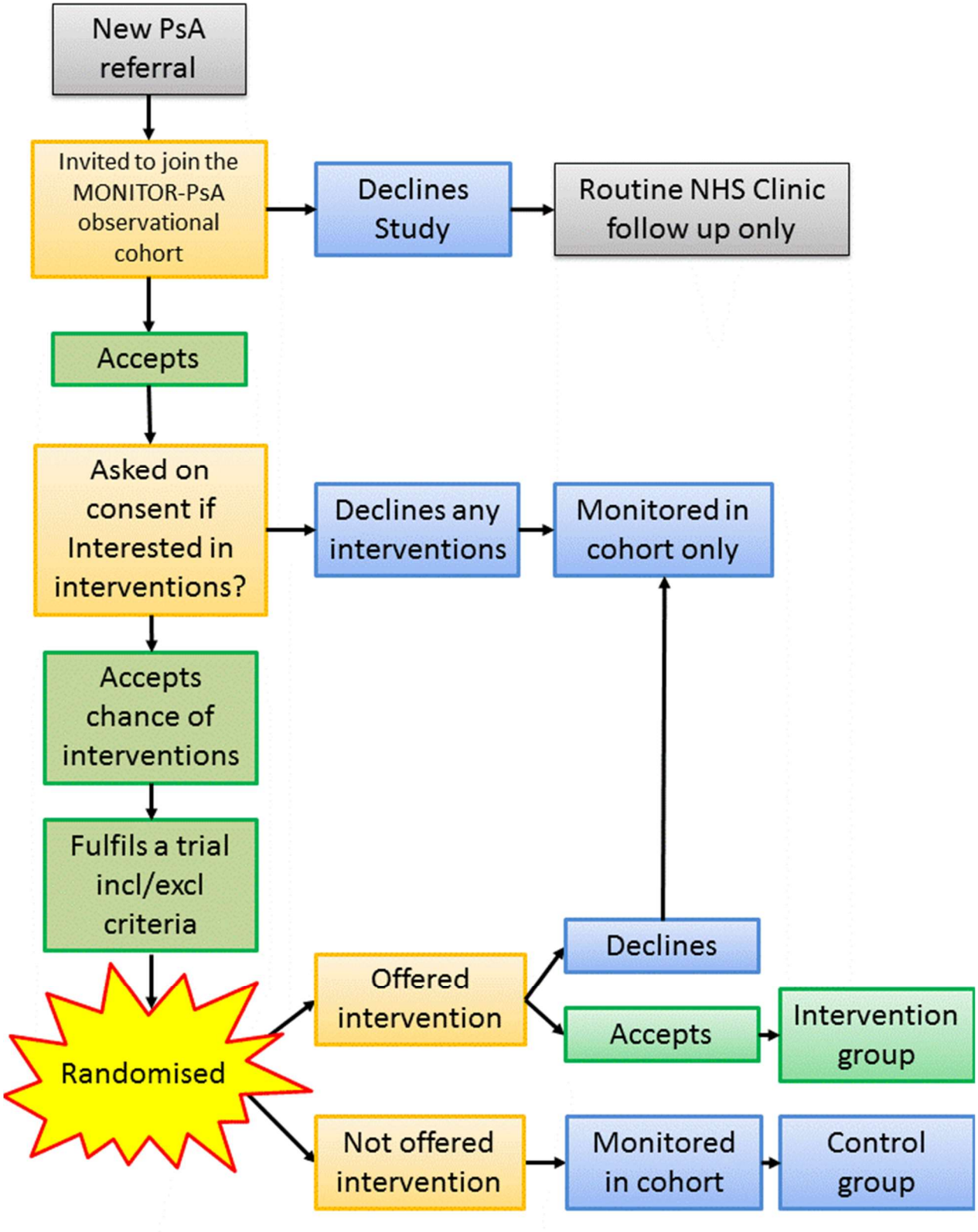
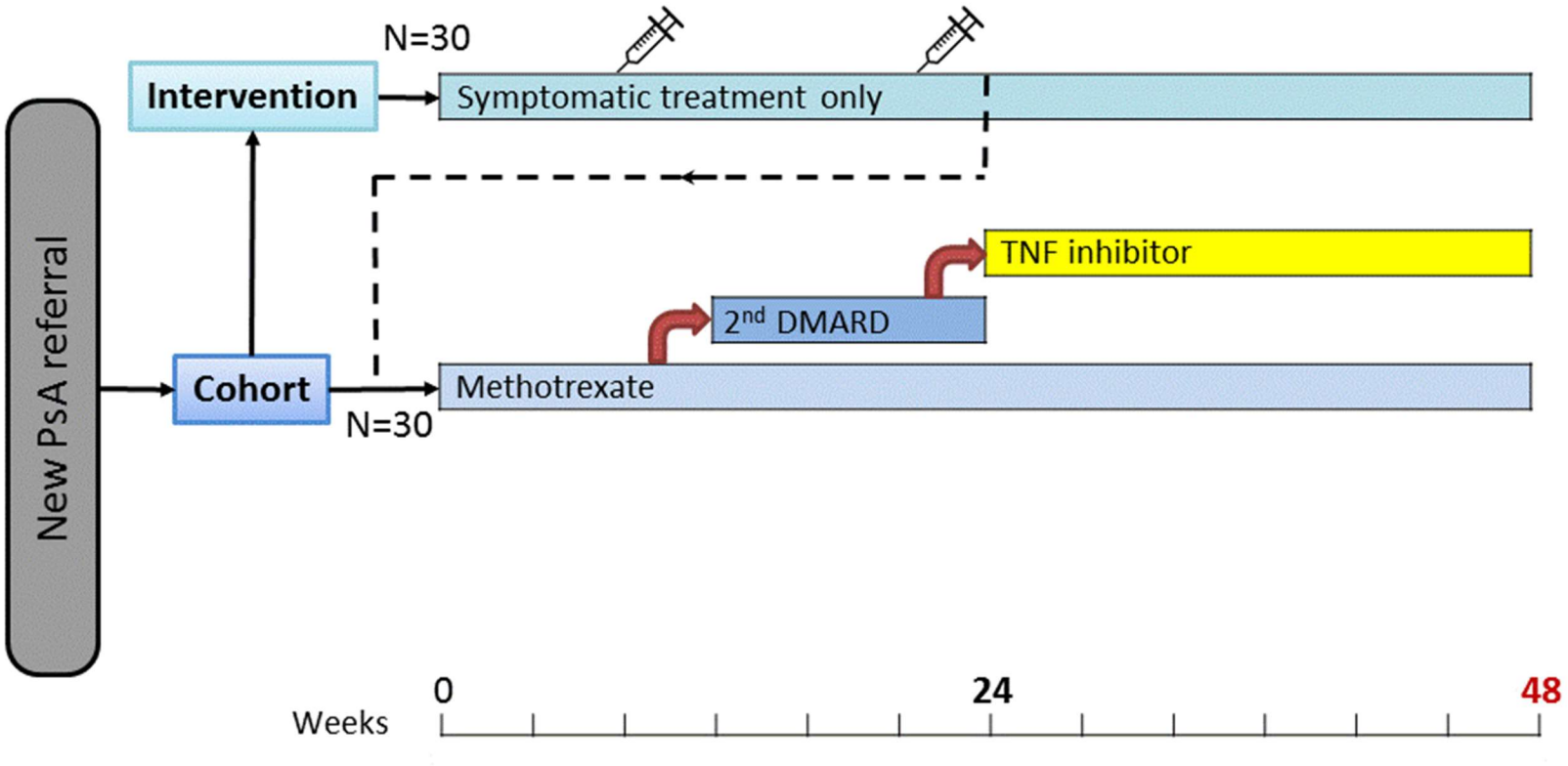
20. APPENDIX A: RECRUITMENT AND INCLUSION TO TRIAL



21. APPENDIX B: TRIAL FLOW CHART



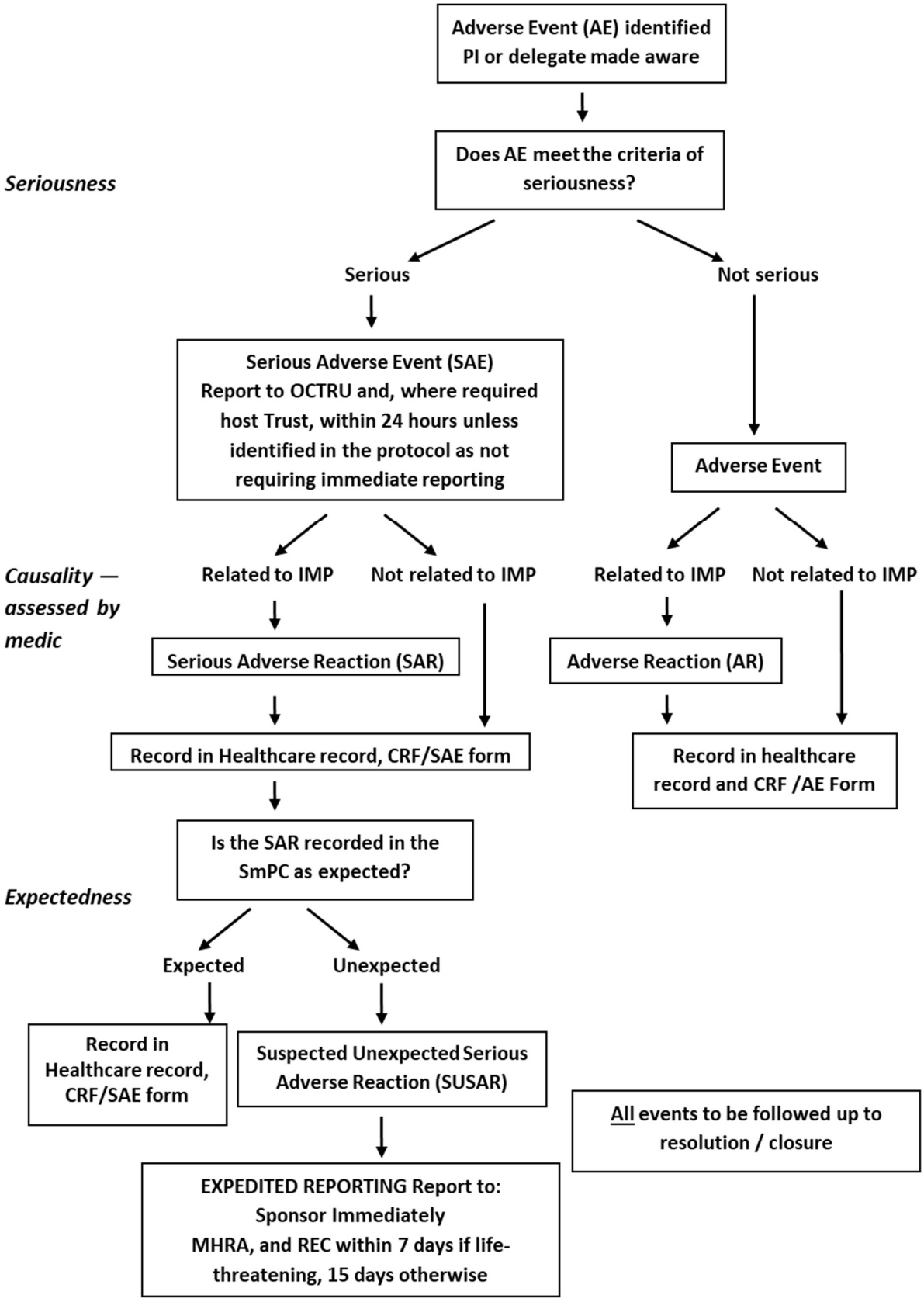
22. APPENDIX C: SCHEDULE OF PROCEDURES

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
Inclusion/exclusion criteria assessment		X				
Medication		X	X	X	X	X
Physical examination		X	X	X	X	X
Routine blood tests (FBC, U&Es, LFTs, CRP)		X	X	X	X	X
Immunology (RF, ACPA)		X				
Radiographs of hands/feet/spine		X				X
Eligibility assessment		X				
Randomisation	X					
Dispensing of drugs within Medication (IA or IM corticosteroids given)		X	X	X	X	
Adherence			X	X	X	X
68/66 Joint count		X	X	X	X	X
Leeds and SPARCC enthesitis index		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

US of joints (interventional arm only)		X				
Adverse event assessments		X	X	X	X	X

Radiographs will be obtained from patient healthcare records as normal care

23. APPENDIX D: SAE REPORTING FLOW CHART



24. APPENDIX E: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1 (non substantial)	V2.1	03 July 2018	Laura Coates	1. Section on Contraception 2. Methylprednisolone Acetate and Triamcinolone will be used as supplied and not diluted
2 (Substantial Amendment)	V3.0	05 Nov 2018	Laura Coates	Not approved
3 (Non substantial)	V3.1	10 Jan 2019	Laura Coates	1. Update to CTRG address 2. Terminology update from 'Participants' to 'Patients' 3. Update Dr Coates phone number 4. Added eGFR to the inclusion criteria section 5. Clarification to section 4.1 and 8.5 - Patients in Arm1 will not receive an Ultrasound scan. 6. Clarification provided in the Inclusion criteria section on contraception. 7. Addition of eGFR to the efficacy bloods within the baseline assessment section. 8. Removal of dilution wording from section 4.1 to be consistent with section 9.1.
4 (Substantial amendment)	V5.0	21Mar 2019	Laura Coates/Yvonne Sinomati	9. 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.
5 (Substantial amendment)	V6.0	27Aug2019	Laura Coates/Yvonne Sinomati	1. Low disease activity (PASDAS) and Low impact of disease (PSAID) removed from Section 4 and 7.2. 'A member of the research team will

				undertake disease activity assessments blinded' added to section 8.4.

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