

Title: A multicentre observational psoriatic arthritis cohort study addressing real-life outcomes of a treat to target approach in routine clinical practice.

Internal Reference Number / Short title: MONITOR PsA – Multicentre ObservatioNal Initiative in Treat to target Outcomes in Psoriatic Arthritis.

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Please declare any/no potential conflicts of interest.

Laura Coates – none

Confidentiality Statement



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

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1 SYNOPSIS

Study Title	A multicentre observational psoriatic arthritis cohort study addressing real-life outcomes of a treat to target approach in routine clinical practice.	
Internal ref. no. / short title	MONITOR PsA – Multicentre ObservatioNal Initiative in Treat to target Outcomes in Psoriatic Arthritis.	
Study Design	Observational cohort study	
Study Participants	Newly diagnosed patients with a diagnosis of psoriatic arthritis	
Planned Sample Size	500	
Sites	5 – 15 Uk sites.	
Planned Study Period	Dec 2017 – December 2024	
	Objectives	Outcome Measures
Primary	To establish the overall clinical effectiveness of a pragmatic treat to target regime utilised in clinical practice	The primary outcome will be the proportion of patients achieving a good response level (reduction from baseline of ≥ 1.6 and final score of $\leq 3.2(1)$) in the PsA Disease Activity Score (PASDAS) at 48 weeks(2).
Key Objectives	Secondary To establish the time to clinical effectiveness of a pragmatic treat to target regime utilised in clinical practice To establish effectiveness of a pragmatic treat to target regime on the new domains of the PsA core set (participation, fatigue and emotional wellbeing) To establish the healthcare costs of a pragmatic treat to target regime utilised in clinical practice To establish the tolerability of the treat to target regime	• Time from baseline to first achieving minimal disease activity (MDA)(3) and PASDAS good response(1) • Proportion achieving PASDAS good response(1) at 24, 48 and 96 weeks • Proportion achieving PASDAS moderate response(1) at 24, 48 and 96 weeks • PASDAS continuous outcome at 24, 48 and 96 weeks • Change in PsA impact of disease (PsAID) score(4) from baseline to follow up • Proportion achieving PsAID patient acceptable symptom state (≤ 4) (4) at follow up • Change in work productivity (absenteeism, presenteeism and productivity loss) as measured by WPAI(5) at follow up • EQ-5D-5L(6) converted into multi-attribute utility scores using established algorithm(7, 8) and resource use data to record direct medical costs and non-medical costs. Unit cost data will be obtained from national databases such as the BNF and PSSRU Costs of Health and Social Care(9). • Side effects reported at each time point, combined with the Treatment satisfaction questionnaire for medication

	To perform exploratory analyses of biological samples for immunophenotyping and genetic data that could in future predict outcome	• Explore immune response in patients with PsA and how this relates to clinical effectiveness with standard therapies.
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2 ABBREVIATIONS

ACPA	Anti-citrullinated peptide antibodies
ALT	alanine aminotransferase
ANA	Antinuclear antibodies
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASMI	Bath ankylosing spondylitis metrology index
BASFI	Bath Ankylosing Spondylitis Functional Index
BSA	Body surface area
BSR	British Society for Rheumatology
CASPAR	CIASsification criteria for Psoriatic Arthritis
CI	Chief Investigator
CRF/eCRF	Case Report Form / electronic Case Report Form
CRP	C-reactive protein
DMARDs/csDMARD/tsDMARD	Disease Modifying Anti-Rheumatic Drugs / Conventional systemic disease-modifying anti-rheumatic drugs / targeted synthetic DMARDs
DSMC	Data & Safety Monitoring Committee
eGFR	Estimated Glomerular Filtration Rate
EMS	Early morning stiffness
EuroQoL	European Quality of Life
EULAR	EUropean League Against Rheumatism
FBC	full blood count
FCS/DMSO	Fetal calf serum/ dimethyl sulfoxide
GCP	Good Clinical Practice
GP	General Practitioner
HAQ	Health assessment questionnaire
HRA	Health Research Authority
HRQoL	Health-related quality of life
IBP	Inflammatory back pain
ICER	Incremental cost-effectiveness ratio
ICF	Informed Consent Form
IPAQ	International physical activity questionnaire
LEI	Leeds enthesitis index
LFTs	Liver function tests
MDA	Minimal disease activity

MONITOR PsA	Multicentre ObservatioNal Initiative in Treat to target Outcomes in Psoriatic Arthritis.
NHS	National Health Service
OCTRU	Oxford Clinical Trials Research Unit
PARS	PsA Ratingen Score
PASDAS	PsA Disease Activity Score
PASI	Psoriasis Area and Severity Index
PIS	Participant/ Patient Information Sheet
PROM	Patient Reported Outcome Measure
PsA	Psoriatic Arthritis
PsAID	Psoriatic Arthritis Impact of Disease
QALY	Quality Adjusted Life Year
RCT	Research Clinical Trial
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RF	Rheumatoid factor
RNHRD	Royal National Hospital for Rheumatic Diseases
SAE	Serious Adverse Event
SF36	Short Form (36) Health Survey
SOP	Standard Operating Procedure
SPARCC	Spondyloarthritis Research Consortium of Canada
SUSAR	Suspected Unexpected Serious Adverse Reaction
SJC	Swollen joint count
TICOPA	Tight control of inflammation in early psoriatic arthritis (See ref 18)
TJC	Tender joint count
TMF	Trial Master File
TNF	Tumour Necrosis Factor
TNFi	Tumour Necrosis Factor inhibitor
TSC	Trial Steering Committee
TSQM	Treatment satisfaction questionnaire for medication
TWiCs	Trials Within Cohorts
U&Es	Urea and electrolytes
VAS	Visual Analogue Scale
VLDA	Very low disease activity
WPAI	Work productivity and activity impairment

3 BACKGROUND AND RATIONALE

Psoriatic Arthritis (PsA) is an inflammatory arthritis estimated to occur in 15% of people with psoriasis(10) affecting around 150,000 people in the UK(11). 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(12, 13). People with PsA have similar functional and quality of life impairment to rheumatoid arthritis(14). PsA is associated with a reduced life expectancy(15) related to the risk of comorbidities, particularly the metabolic syndrome(16). 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(17).

The TICOPA trial was the first to demonstrate improved clinical and patient reported outcomes with a 'treat to target' approach in PsA consisting of 4-weekly review and escalation of treatment aiming for the minimal disease activity (MDA) criteria(18). This led to the 2015 European League Against Rheumatism (EULAR) Treatment recommendations for PsA incorporating as its first recommendation that "treatment should be aimed at reaching the target of remission or, alternatively, minimal/low disease activity, by regular monitoring and appropriate adjustment of therapy"(19).

Despite the evidence(18) and the EULAR recommendations supporting 'treat to target' in PsA (19), it has not been widely implemented due to concerns about feasibility and cost-effectiveness(20). The TICOPA trial estimated an incremental cost-effectiveness ratio (ICER) of £53,948 per quality-adjusted life-year (QALY) with costs related to appointment frequency and prescriptions. Sensitivity analysis using models with fewer appointments for patients in consistent MDA decreased the ICER to ~£30,000 per QALY gained(18). In clinical practice, the 4-weekly review used in the TICOPA trial is not affordable or feasible and is too intensive for patients just starting new therapies or stable in MDA. This cohort will establish a pragmatic feasible 'treat to target' approach in a real-life clinic population which we believe can provide similar clinical and health-related quality of life outcomes to those seen in TICOPA at a lower cost. Dissemination of these results will aid translation of 'treat to target' into clinical practice.

The key outcomes are to establish clinical effectiveness and costs allowing comparison with the TICOPA trial(18). The primary outcome will be the proportion of patients achieving a good response(1) measured by the PsA Disease Activity Score (PASDAS)(2) at 48 weeks. Additional domains including participation, fatigue and emotional wellbeing will be assessed for the first time. Finally the costs of this pragmatic intervention will be established using health economic analysis.

All new referrals with PsA will be approached to enter the cohort. The aim is maximise generalizability to clinical practice when assessing effectiveness of treatment in PsA. All patients will receive treatment as usual following the current British Society for Rheumatology BSR(21) and EULAR guidance(19) as standard of care. Therefore there should be no additional risks or benefits to the participants beyond that in usual care.

This cohort further aims to support other research projects 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. A random group of eligible patients are selected from the cohort to be offered these alternative therapies with other members of the cohort acting as comparative controls. This allows robust generalizability from studies to routine health care. It further avoids attrition and disappointment bias from controls in open label studies, as patients 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(22). 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 trialled(22). Thus participants in the MONITOR cohort will also be asked if they consent to be approached about these trials, if eligible. If consent is granted they may therefore be approached and offered an intervention as part of that trial. These embedded trials will each have their own separate protocols and consent processes.

4 OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Time point(s) of evaluation of this outcome measure (if applicable)
Primary Objective To establish the overall clinical effectiveness of a pragmatic treat to target regime utilised in clinical practice	The primary outcome is the response according to PASDAS(2). This will be reported as the proportion achieving a PASDAS good response(1) at 48 weeks	Clinical assessment, patient questionnaires and blood tests all performed at weeks 0 and 48.
Key Secondary Objectives To establish the time to clinical effectiveness of a pragmatic treat to target regime utilised in clinical practice	- Time from baseline to first achieving minimal disease activity (MDA)(3) and PASDAS good response(1) - Proportion achieving PASDAS good response(1) at 24 and 96 weeks - Proportion achieving PASDAS moderate response(1) at 24, 48 and 96 weeks - PASDAS continuous outcome at 24, 48 and 96 weeks	Clinical assessment, patient questionnaires and blood tests all performed at weeks 0, 24, 48 and 96.
To establish effectiveness of a pragmatic treat to target regime on the new domains of the PsA core set (participation, fatigue and emotional wellbeing)	- Change in PsA impact of disease (PsAID) score(4) from baseline to follow up - Proportion achieving PsAID patient acceptable symptom state (≤ 4)(4) at follow up - Change in work productivity (absenteeism, presenteeism and productivity loss) as measured by WPAI(5) at follow up	Patient questionnaires at weeks 0, 24, 48 and 96 weeks.
To establish the healthcare costs of a pragmatic treat to target regime utilised in clinical practice	EQ-5D-5L(6) converted into multi-attribute utility scores using established algorithm(7, 8) and resource use data to record direct medical costs and non-medical costs. Unit cost data will be obtained from national databases such as the BNF and PSSRU Costs of Health and Social Care(9).	Patient questionnaires and analysis of hospital data at weeks 0, 24, 48 and 96 weeks.

To establish the tolerability of the treat to target regime	Side effects reported at each time point, combined with the Treatment satisfaction questionnaire for medication	Patient questionnaires and analysis of hospital data at weeks 0, 24, 48 and 96 weeks.
To perform exploratory analyses of biological samples for immunophenotyping and genetic data that could in future predict outcome.	Explore immune response in patients with PsA and how this relates to clinical effectiveness with standard therapies.	Blood will be collected at routine visits at weeks 0, 24, 48, 96 weeks and yearly thereafter. Stool samples along with food diary and an International physical activity questionnaire will be collected at routine visits at weeks 0, 24, 48, 96 weeks and yearly thereafter. Surplus synovial fluid and/or tissue from clinically indicated diagnostic or therapeutic procedures will also be collected with consent.

5 STUDY DESIGN

This is an observational cohort study addressing outcomes in patients newly diagnosed with PsA. Participants will be treated with the recommended standard care for PSA. Appendix D details standard care within the NHS for this patient group. Participants will be asked to continue in the cohort throughout the duration of their treatment in the clinic, with visits coinciding with standard healthcare appointments. Participants will be seen every 3 months in year 1, then every 6 months in year 2 and annually thereafter. If participants change therapy additional data will be collected at the time of switch.

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 the participants are seen face-to-face. Therefore participants will need to attend face to face clinic appointment at baseline, 12 weeks, 24 weeks, 36 weeks and 48 weeks. However, if the participants are stable, their disease is under control and they have previously met target MDA, the 36 week assessment could be carried out remotely. Consultations after week 48 should ideally be carried out face to face to allow assessment of key secondary outcomes, particularly at annual visits. However if this is not possible within NHS practice, remote follow up will be permitted.

Data from participant completed questionnaires (patient reported outcome measures (PROMS)), clinical examination and routinely performed blood tests will be recorded at the time of study visits. Where assessments are performed remotely, participants will be asked to complete PROMs online or via postal questionnaires. It will be recorded onto an electronic database which will calculate the composite outcome measures (PASDAS and MDA) automatically.

This is an observational study where all patients will receive standard care and their outcomes will be monitored. It does however form the basis of a TWiCs design and in future it is anticipated that randomised controlled trials (RCTs) will be established within this cohort. The TWiCs design recruits a central cohort having “treatment as usual” with regular observations and adds pragmatic investigations of alternative treatments. A random group of eligible participants are selected from the cohort to be offered these alternative therapies with other members of the cohort acting as comparative controls.

6 PARTICIPANT IDENTIFICATION

6.1 Study Participants

Adult participants with newly diagnosed PsA who have not previously received treatment with synthetic or biologic disease-modifying anti-rheumatic drugs (DMARDs) for their articular disease.

6.2 Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Male or Female
- Aged 18 years or above.
- Clinical diagnosis of PsA based upon the Classification of Psoriatic Arthritis (CASPAR) criteria(23))
- Active PsA defined by ≥ 1 tender or ≥ 1 swollen joint or ≥ 1 enthesis (site of attachment of tendon to bone)
- Not previously received treatment with synthetic or biologic disease-modifying anti-rheumatic drugs (DMARDs) for their articular disease.
- In the Investigator's opinion, is able and willing to comply with all study requirements.

Although not an inclusion criteria for the study, to ensure safe prescription of standard care therapies the following are routinely required in standard care prior to prescribing the appropriate disease modifying drugs used in practice as per current UK guidance:

- 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 during potentially teratogenic DMARD treatment and for 3 months thereafter (or 2 years if received leflunomide unless treated with washout therapy) as in standard practice.
- Women who are pregnant, nursing or planning pregnancy during the following 12 months will only receive DMARDs that are appropriate according to BSR recommendations.
Baseline safety laboratory results within 28 days of baseline fulfilling:
 - a. Haemoglobin >8.5 g/dL
 - b. WBC $>3.5 \times 10^9$ /L
 - c. Neutrophils $>1.5 \times 10^9$ /L
 - d. Platelets $>100 \times 10^9$ /L
 - e. AST or ALT and alkaline phosphatase levels <3 x upper limit of normal

These results will be collected and verified on study entry, but the results do not form a specific inclusion criteria for the cohort itself.

6.3 Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Current or previous treatment of arthritis with synthetic DMARDs (including methotrexate, leflunomide or sulfasalazine) or biologic DMARDs (including TNF, IL12/23 or IL17 inhibitor therapies) or targeted synthetic DMARDs (PDE4 or JAK inhibitor therapies).

- Use of investigational therapies within 1 month or 5 biological half-lives of the baseline study visit (whichever is longer)

7 STUDY PROCEDURES

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

7.1 Recruitment

Potential participants will be identified from new referrals to the rheumatology service, particularly those referred to the early arthritis clinic or dedicated PsA clinic. Patients will be identified and approached initially by their clinical care team and will be given brief information about the study. If 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 7.2, they will be allowed as much time as they wish to consider their participation.

7.2 Screening and Eligibility Assessment

Eligibility will first be assessed when patients are referred to the rheumatology department. Potentially eligible participants will be invited to the early PsA clinic for initial assessment, at the time of their routine visit, and consent into the cohort and for further follow up. If patients decline entry to the study, they will be treated as per usual care in the rheumatology service.

Screening consists only of history taking and physical examination to establish the diagnosis and ensure all inclusion/exclusion criteria are met. This will be performed by members of the research team but in their capacity as the patients clinical care team. Routine safety blood tests will be performed, as part of NHS standard care, to ensure safety on any prescribed disease-modifying therapy but this does not form an exclusion criteria to cohort participation.

7.3 Informed Consent

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

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study 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.

As part of the consent process for the cohort, participants 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.

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 study. 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. One copy will be sent to the study coordinating team in Oxford and one copy will be included in the hospital case notes. The original signed ICF will be retained in the Investigator Site File (ISF).

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

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 of the participant's details will be 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 NHS Digital and other central UK NHS bodies, and to provide other basic study-related information that may be needed for follow up. This will allow the study team to contact participants for future research (if they have consented to this) and to allow possible telephone contact if they do not attend clinic visits.

GPs, or other healthcare professionals, will not be notified routinely of participation in the cohort as normal care is being provided. For those consenting to take part in interventional studies notification will be carried out in accordance with the protocols and consent processes for those further studies.

7.4 Randomisation, blinding and code-breaking

Randomisation for the interventional studies will be carried out if patients have consented to be contacted about and randomised into such studies and if they meet the inclusion/exclusion the relevant study.

Procedures and responsibilities will be study dependent and defined in a Randomisation and, as appropriate, Blinding/Unblinding Plan. Typically randomisation will be undertaken via a centralised service run through the Oxford Clinical Trials Research Unit (OCTRU) who will use computer-generated randomisation allocations using a minimisation approach including a random element will ensure balanced allocations across the treatment groups.

7.5 Baseline Assessments

The following baseline assessments are all performed as standard care and must be performed before participants start on treatment. The following will be assessed for all participants.

- 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)
- Genetic Marker: HLA-B27
- Efficacy bloods: C-reactive protein (CRP) and eGFR
- PsA history: PsA type; symptom onset; diagnosis date; peripheral and back early morning stiffness (EMS); inflammatory back pain (IBP).

- CASPAR Criteria(23):
 - 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:
 - Tender and Swollen Joint Count: 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(24) and Spondyloarthritis Research Consortium of Canada (SPARCC)(25) enthesitis index
 - Psoriasis Area Severity Index (PASI)(26) and body surface area (BSA)(27)
 - Physician's VAS of overall disease activity
 - Bath Ankylosing Spondylitis Metrology Index (BASMI)(28) (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).

In addition to standard NHS care participants will be asked to complete the following patient reported outcomes:

- Global disease activity visual analogue scale (VAS)(31)
- Participant pain VAS
- Health assessment questionnaire (HAQ)(32)
- PsA impact of disease (PsAID)(4)
- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)(33)
- SF36(34)
- EQ-5D-5L(6)
- Work productivity and activity impairment (WPAI)(5)
- BASFI

7.6 Subsequent Visits

Follow up will parallel routine NHS outpatient appointments. Data will be collected at 12, 24, 36, 48, 72 and 96 weeks and annually thereafter for as long as the study is funded. When participants change therapy beyond the first year of the cohort study, additional visits will be performed according to standard care, with suggested assessment visits at 0, 12 weeks, 24 weeks, 48 weeks following the treatment change and annually thereafter. At each visit the following NHS standard care assessments will be performed and the data collected for research (for both cohort and trials within cohort):

- Medical history (update)
- Current treatment for psoriatic arthritis
- Treatment tolerability

- Concomitant medication history (glucocorticoids and non-steroidal anti-inflammatory drugs only)
- Physical examination: pulse; blood pressure; weight
- Safety bloods¹: haemoglobin, WBC, platelet count, neutrophils, ALT.
- Efficacy bloods¹: CRP and eGFR
- Full clinical disease assessment:
 - Tender and Swollen Joint Count: 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(32) and Spondyloarthritis Research Consortium of Canada (SPARCC)(33) enthesitis index
 - Psoriasis Area Severity Index (PASI)(25) and body surface area (BSA)(34)
 - Physician's VAS of overall disease activity

¹See section 7.7 for details.

Participants will be asked to complete the following patient reported outcomes for the purposes of the research:

- Global disease activity visual analogue scale (VAS)(31)
- Participant pain VAS
- Health assessment questionnaire (HAQ)(32)
- PsA impact of disease (PsAID)(4)
- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)(33)
- SF36(34)
- Work productivity and activity impairment (WPAI)(5)
- Health system utilisation data
- Treatment satisfaction questionnaire for medication (TSQM)(35)
- Bath Ankylosing Spondylitis Functional Index (BASFI) Compliance with treatment
- Those participants who have agreed to donate stool sample will additionally be asked to complete:
- Food diary and an International physical activity questionnaire

At certain visits additional assessments will be performed:

- Every 6 months and yearly after week 96
 - EQ-5D-5L(6)
 - Health system utilisation data
- At **baseline and 48 weeks**
 - 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, Week 48 and yearly thereafter
 - 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 weeks

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, paper questionnaires should be provided to the participants to complete and return to the study site by post or where available a web link for online completion sent by email. Assessments after 48 weeks should ideally be carried out face to face to allow assessment of key secondary outcomes, particularly at annual visits. However if this is not possible within NHS practice, remote follow up will be permitted, with PROMs collected online or by postal questionnaires.

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.

7.7 Sample Handling

Routine safety and efficacy blood tests will be performed for all patients receiving disease-modifying therapy as done in standard NHS care (primary or secondary care as per usual practice), with samples handled according to local practice. The results of the routine NHS blood tests will be recorded to monitor safety of the treatment and for the study, so as to calculate composite measures of efficacy.

No additional laboratory tests will be required for this study but patients will be given information and invited to provide additional biological samples (see below).

7.8 Description of procedure

Patient Reported Outcomes

Participants will be asked to complete their patient reported outcomes digitally directly into the study database. They will complete the questionnaires listed above at their study visits and the questionnaires will be automatically scored by the computer and provided to their treating rheumatologist to aid in their management.

Biological sampling

Participants consenting to additional biological sampling will be asked to provide up to 120mls of blood at each study visit. This would be taken at the same time as laboratory blood tests performed in the clinic for safety and efficacy monitoring as part of standard care.

Participants may also be asked to give samples of stool at these visits. Participants will provide stool samples in their own home using containers provided during their clinic visit and these can be delivered to the sites at a visit or sent in the post.

Note: urine samples were also collected under previous versions of the protocol but are no longer to be collected for all new and existing follow up patients.

Those participants who agree to provide a stool sample will also be asked to provide some additional information on diet and exercise patterns via completion of a food diary and an International Physical Activity Questionnaire (IPAQ) to investigate whether knowing the microbiome (the bacteria in and on our body) can help doctors provide the best and safest treatment in psoriatic arthritis. A version of the International Physical Activity Questionnaire that can be completed during a telephone call is also available in case of the need to contact participants remotely. Completion of the food diary and IPAQ is optional.

New participants to the MONITOR study who agree to provide a stool sample will be offered the food diary and IPAQ to complete. Completion of these documents is optional. The food diary and questionnaire require completion 7 days prior to provision of the stool sample and should be returned to the study team in the envelope provided. Where this data is not provided along with the stool sample, it may be requested retrospectively by the site team by email or post using the cover letter for previously provided stool samples.

Participants who have previously provided stool sample(s) will be provided with the food diary and IPAQ to complete, and explanatory cover letter, along with an envelope for return of the completed documents to the study team. Completion of these documents is optional. If the participant would like to complete the food diary and questionnaire they can be returned either at the next clinic appointment or by post.

In some circumstances, participants will also be asked to consent to the collection of surplus samples of synovial fluid where available. Synovial fluid samples would only be taken at the time of arthrocentesis for diagnostic and therapeutic reasons. Up to 100ml is usually aspirated from a large joint such as a knee, only 10mls of which is used for diagnostic culture and microscopy, the remainder being surplus to clinical requirements. If synovial membrane were removed during diagnostic or therapeutic arthroscopy, a small amount (less than 50%) would be studied, once samples had been sent for histology. This material would otherwise be discarded as surplus to clinical requirements.

Serum and synovial fluid will be frozen for analysis of constituents including proteins by ELISA, electrophoresis, mass spectrometry and other biochemical assays. Mononuclear cells will be obtained by density gradient centrifugation separation from blood and synovial fluid. Immunophenotyping by flow cytometry will be carried out at baseline and in-vitro assays will be performed. The remainder of cells will be frozen in FCS/DMSO for batched experiments. DNA and RNA will be extracted for molecular typing of molecules of immunological importance including Human Leukocyte Antigen typing and transcriptomic analysis.

Stool and previously collected urine samples will be studied for biomarkers including genetic and metabolomics analysis of microorganisms potentially influencing the immune system.

Participants may be invited to participate in subsequent ethically approved clinical trials based on phenotyping or genetic data obtained through the biological sampling. These data will be held in pseudoanonymised form and used to assess eligibility for future studies where a participant has consented to this. The link to participant's identifiable information and contact details will be held by the study team and used only where a participant has consented to be contacted about future research. Any future

contact would come from this research team and would make clear participants are under no obligation to participate in any such study.

Samples will be stored frozen in secure research facilities for the duration of the study. Samples will only be identifiable by the participants' study code. The aim of this project is to create a long running cohort and, contingent on further funding being available, it is likely this study would be extended. Any such extension would be notified to the Sponsor, REC and HRA as appropriate.

Following completion of the study, and with patient consent, samples will be used in future ethically approved studies. If an appropriate biobank is identified, samples may be transferred for storage to said biobank. If a participant does not consent to the use of their samples in future research, these will be destroyed in compliance with the Human tissue Act at the end of this study.

Standard Care Other procedures are detailed in Appendix D (Standard NHS Care).

7.9 Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time, with data collected up to the point of withdrawal being retained and used in the analysis as stated in the patient information leaflet. If a participant withdraws consent from the study, their data and samples will be retained and will be included in the final study analysis. If the participant withdraws consent for future samples to be taken, their existing data and samples will be retained and will be included in the final study analysis. If the participant requests for their samples to be destroyed, then the samples will be destroyed alongside all identifiable information.

In addition, the Investigator may discontinue treatment at any time if the Investigator considers it necessary for any reason, including:

- Pregnancy
- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- Withdrawal of Consent
- Loss to follow up

Withdrawal from the study will not result in exclusion of the existing data for that participant from analysis. Withdrawal from the cohort will result in withdrawal from all linked investigational studies. Participants will not be replaced. The reason for withdrawal, if known, will be recorded in the Case Report Form (CRF).

7.10 Definition of End of Study

The end of study is once all data has been entered and data queries resolved.

8 SAFETY REPORTING

8.1 Definition of Serious Adverse Events

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.

8.2 Reporting Procedures for Serious Adverse Events

Only serious adverse events (SAE) occurring to a participant where in the opinion of the CI the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures will be reported to the REC .

Reports of related and unexpected SAEs should be submitted within 15 working days of the CI becoming aware of the event and should be reported to the Research Ethics Committee (REC) that gave a favourable opinion of the study. This will be undertaken by the MONITOR-PsA study management team at OCTRU.

Sites are to report any SAEs occurring after consent until the end of study follow up that are both related and unexpected to the MONITOR-PsA study management team via completion of the MONITOR-PsA SAE form which must be emailed to monitorpsa@ndorms.ox.ac.uk. Information to be provided includes details of the event, start and end dates, action taken, outcome, seriousness criteria, causality in the opinion of the investigator.

These SAEs must be reported within a very short period of time and under no circumstances should this exceed 24 hours following knowledge of the SAE. Any follow up information that becomes available must also be submitted by email to monitorpsa@ndorms.ox.ac.uk within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

It is a requirement of one of the funders of this research that any adverse drug reactions (ADRs) to certolizumab (Cimzia) are reported to UCB pharma for 12 months from the finalised contract. Any ADRs related to certolizumab should be reported, using the Cimzia ADR form, by email to monitorpsa@ndorms.ox.ac.uk within 24 hours of the information becoming available and the study management team will send these on to UCB. Only anonymized information will be collected and sent to UCB pharma.

9 STATISTICS AND ANALYSIS

9.1 Description of Statistical Methods

The primary analysis will report the outcomes together with 95% confidence intervals. The estimates for the participants receiving the standard treatment (pragmatic 'step-up' 'treat to target' treatment) in MONITOR will be compared informally to the outcomes for the relevant trial arms of the TICOPA trial (i.e. no formal statistical tests will be performed). Supplementary analysis will be undertaken to explore the many baseline prognostic factors in order to examine which patients most benefit from this treatment and whether important subgroups can be defined.

9.2 The Number of Participants

At present, we aim to recruit 500 patients to take part in the cohort. Some of the eligible patients may be offered alternative treatments as part of related RCTs. All will receive standard care up to the point of receiving such an alternative treatment. The number of patients actually receiving the standard treatment (pragmatic 'step up' 'treat to target' treatment) within the cohort is likely to be around 200 patients, based on the other trials planned within this cohort. All participants in the cohort and associated trials will be followed up at the same time-points. This should be sufficient to allow calculation of a robust confidence interval around the primary outcome (proportion of patients achieving a PASDAS good response (1) at 48 weeks).

9.3 Analysis of Outcome Measures

Analysis will be undertaken within OCTRU supervised by the statistician for the study. The primary endpoint is the proportion of patients achieving the PASDAS 'good' response(1) at 48 weeks. The PASDAS is a composite score including both clinical assessment and patient reported outcomes(2). It is calculated as $((0.18 \times \text{physician global VAS}) + (0.159 \times \text{patient global VAS}) - (0.253 \times \text{VSF36-PCS}) + (0.101 \times \text{LN (SJC+1)}) + (0.048 \times \text{LN (TJC+1)}) + (0.23 \times \text{LN (Leeds enthesitis index +1)}) + (0.37 \times \text{LN (tender dactylitis count+1)}) + (0.102 \times \text{LN (CRP+1)}) + 2) \times 1.5$.

PASDAS response are calculated as follows:

	Improvement		
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

The results will be discussed in the context of the TICOPA trial(18) (n=206) to see if they are consistent. The patients recruited early in the course of the study who therefore have longer term follow-up data will enable us to explore durability of the response.

Key secondary endpoints include:

- Time from baseline to first achieving MDA(3) and PASDAS good response(1)
- Proportion achieving PASDAS good response(1) at 24, 48 and 96 weeks
- Proportion achieving PASDAS moderate response(1) at 24,48 or 96 weeks
- PASDAS continuous outcome at 24, 48 and 96 weeks

- Healthcare costs and QALY gained (see below)

Exploratory outcomes (not available in TICOPA dataset) will include:

- Change in PsA impact of disease (PsAID) score(4) from baseline to 48 weeks
- Proportion achieving PsAID participant acceptable symptom state (≤ 4)(4) at 48 weeks
- Change in work productivity(5) (absenteeism, presenteeism and productivity loss) at 24 and 48 weeks

The primary analysis will report the outcomes together with 95% confidence intervals. The estimates for the participants receiving the standard treatment (pragmatic 'step-up' 'treat to target' treatment) in MONITOR will be compared informally to the outcomes for the relevant trial arms of the TICOPA trial (i.e. no formal statistical tests will be performed). Supplementary analysis will be undertaken to explore the many baseline prognostic factors in order to examine which patients most benefit from this treatment and whether important subgroups can be defined

Health Economic issues

In TICOPA, EQ-5D at 48 weeks and healthcare utilisation questionnaires throughout the trial were used to calculate the cost per QALY in each arm and calculate an ICER(18). For this analysis, HRQoL data (EQ-5D-5L (6)) and resource use data will be collected in order to compare with the TICOPA cohort in a descriptive and informative way.

Primary, Community and Social care service use will be collected at 24 weeks and 48 weeks using self-reported questionnaires. The data collected will 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(9). HRQoL will be estimated using the EuroQoL (EQ-5D-5L (6)). Trial participants will be asked to complete this 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(7, 8). The economic analysis will be conducted from a UK NHS and Personal Social Services perspective (PSS) using the cohort data(36).

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

Missing data will be minimised by careful study conduct and data management. The importance of data collected even after missed appointment or withdrawal from trial treatment will be emphasised to participants and trial staff. Missing data will be described with reasons given where available; the number and percentage of individuals in the missing category will be presented (and by treatment arm for Trials Within Cohort). 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.

10 DATA MANAGEMENT

10.1 Source Data

Source documents are where data are first recorded, and from which participants' eCRF/CRF 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 eCRF/CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

eCRF/CRF entries will be considered source data if the eCRF/CRF 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 consent, the participant will be referred to by the trial participant number/code, not by name.

10.2 Access to Data

Direct access will be granted to authorised representatives from regulatory bodies, the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations. All data and documentation will be stored in accordance with regulatory requirements and access to the data will be restricted to authorised study personnel once participants have consented. OCTRU will securely hold the database.

10.3 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. 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 databases). Participants who opt for online completion will be sent a link and asked to enter their participant ID. 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. To identify manual entry errors a 10% double entry check will be carried out at regular intervals during the data collection phase of the study.

Study documentation must be retained for 15 years after completion of study-related activities. Collaborating sites are delegated the responsibility of archiving local essential documents (including the Investigator Site File) in an appropriate secure environment. The study office will archive the central Trial Master File 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 and patient contact details, the participant will be referred to by the study participant number/code, not by name. Identifiable contact information will be stored separately from study data.

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.

Oxford, Coventry, Newcastle and any other sites except Bath and Cambridge: Patients 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 secure University of Oxford facility at the John Radcliffe Hospital alongside physician entered data. 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: Prior to August 2022: Patients 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 physician entered data. 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. The entirety of the study-related clinical data can be securely sent via encrypted electronic transfer from Meridian to the sponsor in Oxford for storage and analysis. 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 (Meridian).

August 2022 onwards: site will use the OCTRU database systems detailed above.

Cambridge: Patients 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. With the agreement of the TMG, the site may also enter some data directly into the OCTRU OpenClinica database.

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

11 STUDY OVERSIGHT

The day-to-day management of the study will be the responsibility of the Study Manager, supported by the OCTRU administrative staff. This will be overseen by the Study Management Group, who will meet monthly to assess progress. It will also be the responsibility of the Study Manager to undertake training of the research staff at each of the study centres. The study statistician and health economist will be closely involved in setting up data capture systems, design of databases and clinical reporting forms. A Trial Steering Committee (TSC) and an Independent Data & Safety Monitoring Committee (DSMC) will be set up to cover this cohort study and subsequent interventional studies that are related to it.

11.1 Study Supervision

The TSC, which includes independent members, provides overall supervision of the study on behalf of the funder. Its terms of reference will be agreed with the funder and will be drawn up in a TSC charter which will outline its roles and responsibilities. Meetings of the TSC will take place at least once a year during the recruitment period.

An outline of the remit of the TSC is to:

- monitor and supervise the progress of the study towards its interim and overall objectives,
- review at regular intervals relevant information from other sources,
- consider the recommendations of the DSMC,
- inform the funding body on the progress of the study.

The DSMC is a group of independent experts external to the study who assess the progress, conduct, participant safety and, if required critical endpoints of a clinical trial.

The DSMC will agree and adopt an appropriate charter that defines its terms of reference and operation in relation to oversight of the study. They will not be asked to perform any formal interim analyses of effectiveness. They will, however, review accruing data, summaries of the data presented by treatment group, and will assess the screening algorithm against the eligibility criteria. They will also consider emerging evidence from other related research and review related SAEs that have been reported. They may advise the chair of the Study Steering Committee at any time if, in their view, the study (or embedded trial) should be stopped for ethical reasons, including concerns about participant safety. DSMC meetings will be held at least annually during the recruitment phase of the study. Full details including names will be included in the DSMC charter.

The TSC and DSMC for the study will also cover any embedded trials within the cohort to allow cohesive review of any safety issues.

11.2 Quality Control

We will institute a rigorous programme of quality control. The study manager/coordinator will be responsible for ensuring adherence to the trial protocols at the trial sites. Quality assurance checks will be undertaken by OCTRU to ensure integrity of randomisation, study entry procedures and data collection. OCTRU has a quality assurance manager who will monitor this study by conducting regular (at least once in the lifetime of the study, more if deemed necessary) inspections of the Trial Master File (TMF). Furthermore the processes of consenting, randomisation, registration, provision of information and



provision of treatment will be monitored. Written reports will be produced for the TSC, informing them if any corrective action is required.

The study may be monitored, or audited in accordance with the current approved protocol, Good Clinical Practice (GCP), relevant regulations and standard operating procedures. 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 on-site monitoring.

12 QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. 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 on-site monitoring.

12.1. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) 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 study 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.

12.2. SERIOUS BREACHES

A "serious breach" is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

- (a) the safety or physical or mental integrity of the trial subjects; or
- (b) the scientific value of the research.

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 approving REC committee and the relevant NHS host organisation within seven calendar days.

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

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Declaration of Helsinki

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

13.2 Guidelines for Good Clinical Practice

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

13.3 Approvals

The protocol, ICF, PIS and any proposed advertising material will be submitted to an appropriate REC, and Health Research Authority (HRA) 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.

13.4 Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

13.5 Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all study documents and any electronic database, with the exception of the CRF, where participant initials may be added. Participants contact details will be stored securely at the Oxford Clinical Trials Research Unit to allow contact of participants for future studies if the participant consents to this. All documents will be stored securely and only accessible by study staff and authorised personnel. The study 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 database 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.

13.6 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. However we anticipate that all study visits will be alongside standard clinical care appointments.

13.7 Other Ethical Considerations

Vulnerable participants and participants who are not able to consent for themselves will not be recruited to this cohort study. Key information from PROMS will be available to the treating clinical care



team at the patient's visits to allow accurate assessment of disease activity and impact. This will allow appropriate treatment decisions to be made according to standard clinical care. Information regarding this is included in the PIS. Results from the exploratory biological sampling will not be made available to the participants as these are exploratory only and could not, at present, be used to clinical benefit.

14 FINANCE AND INSURANCE

14.1 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 and research grants from Janssen-Cilag Ltd, UCB Biopharma SRL and AbbVie Ltd through the University of Oxford.

14.2 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.

15 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.

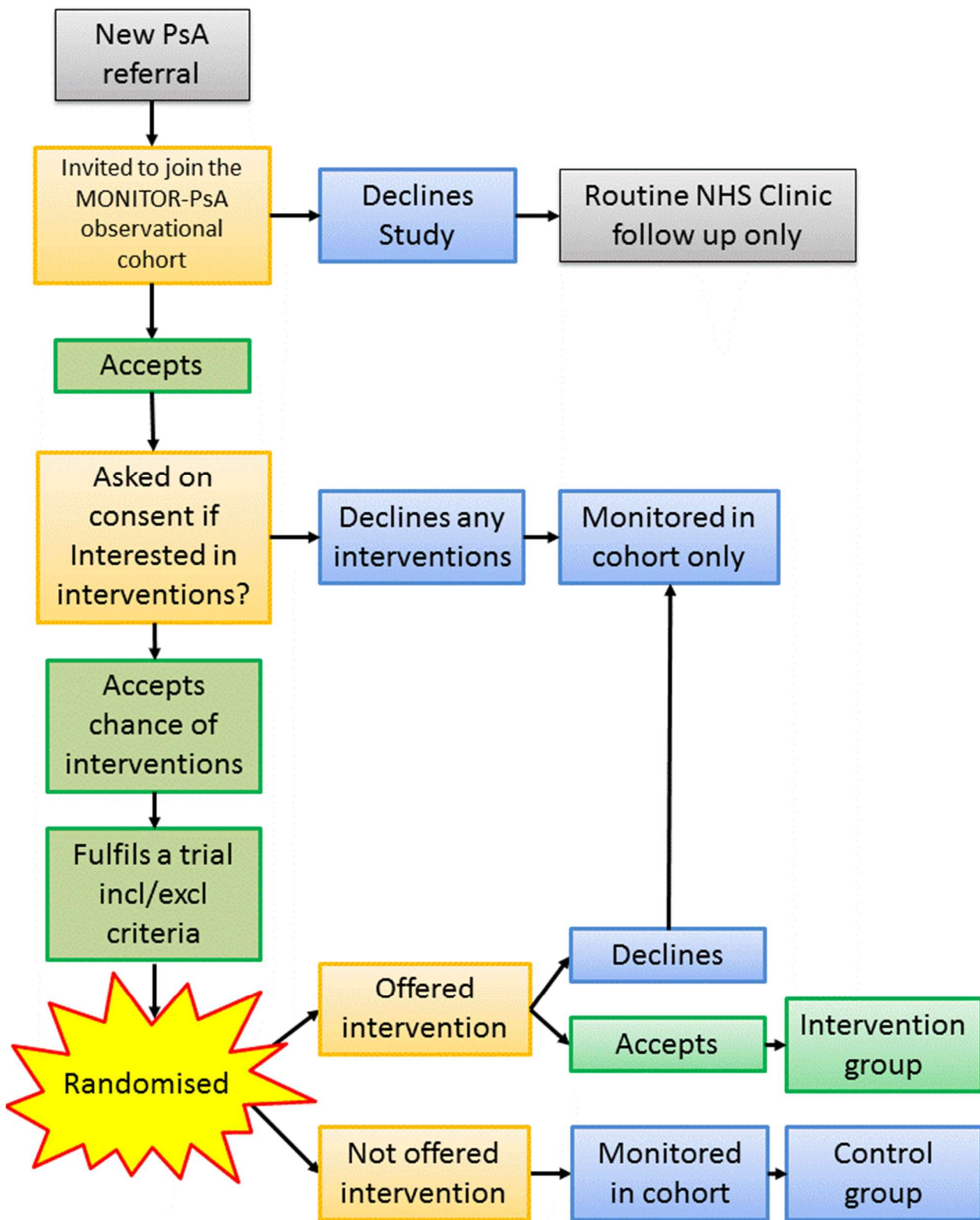
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17 APPENDIX A: STUDY FLOW CHART



18 APPENDIX B: SCHEDULE OF STUDY PROCEDURES

Procedures	Visits							Continuing Annually (after 96 weeks)
	Baseline cohort							
	Week 0	Week 12	Week 24	Week 36 #	Week 48	Week 72	Week 96	
*Informed consent	X							
*Demographics	X							
Medical history	X	X	X	X	X	X	X	X
Medications	X	X	X	X	X	X	X	X
*Physical examination	X	X	X	X/^	X	X	X	X
Routine blood tests ¹ (FBC, U&Es, LFTs, CRP and eGFR)	X	X	X	X	X	X	X	X
Immunology (RF, ACPA, ANA)	X							
Radiographs of hands/feet/spine	X				X			
*Eligibility assessment	X							
Adherence		X	X	X	X	X	X	X
*68/66 Joint count	X	X	X	X /^	X	X	X	X
*Leeds and SPARCC enthesitis index	X	X	X	X /^	X	X	X	X
*Dactylitis count	X	X	X	X /^	X	X	X	X
*Psoriasis assessment (PASI and BSA)	X	X	X	X /^	X	X	X	X
*Physician VAS	X	X	X	X /^	X	X	X	X
*Metrology with BASMI (if axial involvement)	X				X		X	X
*Patient questionnaires (VAS, HAQ, SF36, PsAID, WPAI, BASDAI, BASFI)	X	X	X	X	X	X	X	X
*TSQM questionnaire		X	X	X	X	X	X	X

*EQ-5D-5L questionnaire	X		X		X	X	X	X
*Healthcare utilisation data			X		X	X	X	X
*Adverse event assessments		X	X	X	X	X	X	X
Food diary and IPAQ (Optional for those patients who provide stool samples).	X		X		X		X	X

Items marked with an asterisk are research only procedures. Although clinical assessments are often performed in routine care, they are not universally standard practice.

¹ For information on routine blood tests please refer to the Sample handling section 7.7.

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.

Radiographs will be obtained from patient healthcare records as normal care.

19 APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	V4.0	06Nov2018	Yvonne Sinomati	Pregnancy statement has been removed from the exclusion criteria and moved to 'Although not an inclusion criteria for the study...' section which is under the inclusion criteria section. Addition of eGFR and BASFI. Removal of Health System Utilisation Data from Baseline Assessments and added to 12-24 Months. Reference to the Clinical dataset form has been removed Appendix criteria updated to include week 72 and 96
2	V5.0	21Mar2019	Laura Coates/Yvonne Sinomati	Changes to Data Protection, addition of Coventry and Newcastle site, 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. Addition of Genetic Markers to the Baseline Assessment section.
3	V6.0	24Jun2020	Yvonne Sinomati	Removal of study sites section on page 5 as it is a duplication of sites in the section below. In the sites section the hospital addresses have been updated on page 5. Under Study design section 5 and the Subsequent section 7.6 paragraph added: the participant assessment at 36 week can be carried out remotely if the patient is stable, their disease is under control and they have previously met target MDA, and is unable to be reviewed within the hospital. After 48 weeks all visits should be carried out face to face, however, if not possible remote follow up will be permitted. Appendix B: The schedule of study procedures has been updated to reflect this and a footnote has been added to refer to the sample handling section 7.7. Section 7.6 'Subsequent visits' updated to accommodate visits in weeks not months.

				In section 7.6 a reference has been added that refers to section 7.7. Section 5, page 13 clarification of how PROMs will be sent in the case of remote appointments. Clarification added to Section 7.7 (primary or secondary care as per usual practice). Minor typographical corrections. Abbreviations corrected in table 2 for HAQ and PSAID. Abbreviation changed from PSAID to PsAID throughout the text. Abbreviations throughout the text have been added to section2.
4	V8.0 (V7.0 not used)	06Oct2021	Yvonne Sinomati & Anne Francis	Addition of data collection (International Physical Activity Questionnaire and food diary) to support analysis of microbiome in stool samples. Addition of information about creation, storage and sharing of study datasets. Clarification of SAE reporting procedures Correction to Schedule to match body of protocol Change to planned end date of study. Change to number of participating sites. Correction to archiving period to match that on the PIS. Information on sample retention on withdrawal added. Research grants from Janssen-Cilag Ltd and UCB Biopharma SRL through the University of Oxford added into the Protocol. New contact details added for CTRG, now rebranded as Research Governance, Ethics and Assurance Team.
5	V9.0	21Sep2022	Ioana Marian & Yvonne Sinomati	Synopsis table; '48 weeks' added to the PASDAS continuous outcome at PsA Disease Activity Score within the Primary section. (PASDAS) 24, 48 and 96 weeks added to the secondary objectives and also to section 4.

				Removed reference to 'urine' as no longer being collected as part of Biological sampling for new and existing follow up patients. Section 8.2 reporting of Cimzia ADR information. Section 9.3, Key secondary endpoint section has been updated. Section 10.3, Bath site will now use OCTR database system and Cambridge site will enter some data into OpenClinica. Adverse event assessment removed from the baseline section in Appendix B.
6	V10.0	To be added	Anne Francis/Yvonne Sinomati	Planned end date changed to December 2024. AbbVie added as a funder to the funding sections. Section 7.6 clarified that data being collected for as long as the study is funded. Section 7.6 & Appendix B for EQ5D-5L and HUD; added yearly after week 96 in line with App B. Changed the Radiograph timepoints to Baseline and week 48 only.

20 APPENDIX D: NHS CLINIC PROTOCOL

This appendix includes the current NHS PsA treatment protocol as finalised in September 2017. If new information becomes available about treatment and/or new treatments become approved, this will be updated in keeping with local and national guidance.

1) Psoriatic Arthritis Treatment Protocol

Dr Laura Coates, NIHR Clinician Scientist, University of Oxford

Professor Paul Bowness, Consultant Rheumatologist, Oxford University Hospitals

Dr Deepak Jadon, Consultant Rheumatologist, Cambridge University Hospitals

Dr William Tillett, Consultant Rheumatologist, Royal National Hospitals for the Rheumatic Diseases, Bath.

2) Introduction

This clinic protocol for the treatment of patients with Psoriatic Arthritis (PsA) is based on current treatment recommendations but also remains compliant with current National Institute of Health and Clinical Excellence (NICE) recommendations. This protocol provides guidance on possible treatment options including conventional systemic disease-modifying anti-rheumatic drugs (csDMARDs), biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) but still allows physician discretion dependent on individual patient circumstances and wishes.

3) Psoriatic Arthritis (PsA)

PsA is an inflammatory arthritis associated with skin psoriasis. The prevalence of psoriasis in the general population is estimated at 2-3%. The prevalence of inflammatory arthritis in people with psoriasis has been reported from 6% to 42%. A recent study of incidence of PsA reported an overall age and sex adjusted annual incidence of 7.2 per 100,000 population with a greater incidence in men than women. The course of PsA is variable and unpredictable ranging from mild non-destructive disease to severe debilitating erosive arthropathy which can lead to chronic joint damage (37). Furthermore, PsA causes an increase in disability and its impact in quality of life is comparable to that caused by rheumatoid arthritis (RA) (14).

4) Limitations

The following algorithm is designed for patients with predominant peripheral musculoskeletal involvement. Patients with significant axial disease should be treated as other axial spondyloarthritis (AxSpA) patients following appropriate NICE guidance as standard synthetic DMARDs are not efficacious in this subgroup.

5) Assessment

Treatment is planned using a treat to target approach following current EULAR recommendations. All patients should be assessed every 3-6 months using the minimal disease activity criteria.

Tender joint count (68)	≤1
Swollen joint count (66)	≤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

In keeping with the EULAR and current International Treat to Target recommendations, the main target should be remission as measured by the Very Low Disease Activity (VLDA) criteria where all 7 of the above items are fulfilled. However an acceptable alternative target is Minimal Disease Activity (MDA) where 5 of the above 7 items are fulfilled. For bDMARDs, response should also be recorded using the PsARC criteria to fulfil NICE guidelines on the prescriptions of these therapies. The timing of this assessment varies by drug (TNF inhibitors 12 weeks, apremilast and secukinumab 16 weeks, ustekinumab 24 weeks).

6) Timing of assessments

Providing that new therapies can be tolerated by the patient and do not cause significant toxicity, such that patients are unwilling to continue with treatment or that treatment must be stopped due to safety concerns, a trial of a minimum of 12 weeks therapy should be given before changing or adding an alternative DMARD.

If an assessment is performed after 12 weeks on a new therapy and they have reached the target of treatment, then this should be continued. If they have not achieved MDA but have shown significant improvement since starting the new therapy (a reduction in tender and swollen joint counts of at least 20%) then treatment should be continued for a further 12 weeks before a repeat assessment. If they have not responded significantly, then the next step in the treatment protocol should be offered.

For bDMARDs, response must be recorded using the PsARC criteria to fulfil NICE guidelines on the prescriptions of these therapies. The timing of this assessment varies by drug (TNF inhibitors 12 weeks, apremilast and secukinumab 16 weeks, ustekinumab 24 weeks). If patients do not achieve a PsARC response, then their treatment should not usually be continued.

7) Treatment choice

7.1 Methotrexate - First line treatment unless contraindicated

In line with the EULAR recommendations, methotrexate will usually be the first line treatment for PsA unless contraindicated. Treatment will be given either orally or by subcutaneous injection after discussion between doctor and patient and dependent on local protocols. In addition to the prescription for methotrexate, oral folic acid should be prescribed whilst patients are receiving methotrexate in line with local prescribing policies. Patients prescribed parenteral methotrexate will use the same dosing regimen as for oral therapy. In some cases parenteral methotrexate may be tried as a second line therapy if oral methotrexate is not tolerated or not effective.

Treatment will usually be initiated at 15mg/week for the first 4 weeks, escalating to 20mg/week for 4 weeks and then 25mg/week as tolerated. If there are concerns about toxicity, a slower escalation of dose could be considered. In the event of minor side effects, if a patient is unable to tolerate the dose of the drug defined in the protocol due to toxicity or intolerance, then the highest tolerable dose should be maintained, and the reason for this documented in the notes. In the case of major problems with intolerance or toxicity, this therapy should be stopped and the next step in the protocol should be started.

7.2 Sulfasalazine or leflunomide – Second line treatment, First line if MTX contraindicated, 3rd line if biologics not used

If methotrexate is contraindicated or if there is no response to methotrexate, treatment with either sulfasalazine or leflunomide should be considered. The choice between sulfasalazine and leflunomide should be made by the treating physician based on their assessment of the individual patient the patient's co-morbidities (if any) and the patient's choice. The decision of whether to continue methotrexate in addition to a second DMARD should be made with the individual patients dependent on the efficacy and tolerability experienced with methotrexate previously.

Sulfasalazine – Sulfasalazine should be given orally with an initial increasing dose (500mg od for 1 week, 500mg bd for 1 week, 1g mane and 500mg pm for 1 week and 1g bd thereafter) aiming for an initial therapeutic dose of 1g bd. At the individual physician's discretion, dose can be increased further to a maximum of 40mg/kg/day if required. In the event of minor side effects, if a patient is unable to tolerate the dose of the drug defined in the protocol due to toxicity or intolerance, then the highest tolerable dose should be maintained, and the reason for this documented in the notes. In the case of major problems with intolerance or toxicity, this therapy should be stopped and the next step in the protocol should be started.

Leflunomide - If leflunomide is chosen, it should be started at a dose of 10mg daily, increasing to 20mg daily after 4 weeks if tolerated. In the event of minor side effects, if a patient is unable to tolerate the dose of the drug defined in the protocol due to toxicity or intolerance, then the highest tolerable dose should be maintained, and the reason for this documented in the notes. In the case of major problems with intolerance or toxicity, this therapy should be stopped and the next step in the protocol should be started.

7.3 TNF inhibitors – Third line treatment following NICE guidelines

TNF inhibitors should be usually be used as a third line therapy, if the NICE criteria for the use of these drugs are met and there are no contraindications for their use. It is recommended that all patients should be screened for mycobacterial infection prior to commencing TNF inhibitor therapy. The use of biologic drugs will only be permitted following the NICE guidelines for use of anti-TNF treatment in PsA or following an individual funding request. Patients must fulfil the NICE criteria of active disease (>3 tender and >3 swollen joints) and previous failure of at least 2 standard DMARDs. The choice of TNF inhibitor will be made in collaboration with the patient taking into account any individual patient comorbidities. Choices include adalimumab, certolizumab, etanercept, golimumab or infliximab. Dependent on local prescribing guidelines, approved biosimilars of these therapies may be used. The choice of TNF inhibitor should be based on a decision between patient and physician based on that individual's circumstances also remembering that NICE guidelines state that normally the least expensive of these drugs should be used.

There are some differences between the TNF inhibitors in terms of efficacy for extra-articular manifestations and safety issues which should be considered:

- Etanercept has likely to be lower risk for reactivation of TB as it is less likely to disrupt granuloma and has the shortest half-life so may be preferable in such high risk patients.
- Infliximab also has a licence for the treatment of inflammatory bowel disease (Crohns and ulcerative colitis [UC] in adults and paediatrics) and has the significant evidence for efficacy in the treatment of uveitis
- Adalimumab also has a licence for treatment of inflammatory bowel disease (Crohns and UC in adults and Crohns in paediatrics) and a licence for treatment of uveitis.
- Golimumab also has a licence for treatment of UC.

TNF inhibitors will be given for 12 weeks following the dose regimes below and then response will be assessed. Providing that the drug can be tolerated by the patient and does not cause significant toxicity such that patients are unwilling to continue with treatment or that treatment must be stopped due to safety concerns, a trial of a minimum of 12 weeks therapy should be given before changing or adding an alternative DMARD.

Adalimumab – given at a dose of 40mg every other week by subcutaneous injection

Certolizumab – given at a dose of 200mg every other week by subcutaneous injection after an initial loading dose of 400mg at weeks 0, 2 and 4.

Etanercept – given at a dose of 50mg weekly (or 25mg twice weekly) by subcutaneous injection

Golimumab – given at a dose of 50mg every four weeks unless the patient weighs over 100kg in which case the higher 100mg dose will be used.

Infliximab – given at a dose of 5mg/kg every 8 weeks intravenously after an initial loading dose at weeks 0, 2 and 6.

7.4 Therapy in patients where TNFi contraindicated

Contraindications and cautions related to the use of TNF inhibitors are listed in the table below

	Contraindicated	Use with caution
Infection	Active infection	high risk of infection (chronic infected leg ulcers, recent septic arthritis, persistent or recurrent infections, indwelling urinary catheter, bronchiectasis, hypogammaglobulinaemia)
TB	Active TB	Prophylactic anti-TB therapy should be considered for patients with latent TB prior to starting treatment with TNF inhibitors.
Hepatitis B/C	Untreated active hepatitis B/C	Active/previous hepatitis B/C – co-manage with appropriate specialists

HIV	Untreated HIV with significant immunosuppression	Treated HIV – co-manage with appropriate specialists
Malignancy	Active malignancy	Previous malignancy or pre-malignant conditions
Demyelination	Diagnosis of MS	Other demyelinating conditions
Cardiac failure	Moderate/severe (grade 3/4 NYHA) cardiac failure	Mild (grade 1/2 NYHA) cardiac failure
Conception/pregnancy		If risk of stopping treatment are high.
Interstitial lung disease		Pre-existing ILD

If there are contraindications to the use of TNF inhibitors or a patient refuses these, alternative treatments should be considered. Currently NICE approved treatments would be either ustekinumab or apremilast, however secukinumab is likely to be given a positive decision in May 2017 so is included below. The choice between these agents should be made by the treating physician in consultation with the patient and the nature of the comorbidities will influence that choice. Further details are given under the individual drugs below.

7.5 Post-TNF inhibitor

If the patient does not respond to the initial TNF inhibitor, an alternative biologic may be used. In the majority of cases, a second-line TNF inhibitor therapy will be chosen and ideally it will have an alternative mode of action to the first TNF therapy (i.e. switch from monoclonal antibody to receptor blocker or vice versa). In some cases, another therapy with a completely different mode of action (e.g. IL12/23 inhibitor, apremilast or IL17 inhibitor when available) will be chosen. This decision will be based on a decision between patient and physician based on that individual's circumstances. Further details are given under the individual drugs below. In the case of major problems with intolerance or toxicity (see above) during the 12 week trial, therapy should be stopped and an alternative TNF inhibitor should be started.

7.6 Ustekinumab

Ustekinumab is an IL12/23 inhibitor that targets the common p40 subunit on these molecules. According to NICE technology appraisal, ustekinumab can only be used in patients who have a contraindication to TNF inhibitors or who have failed treatment with a TNF inhibitor. As for TNF inhibitors, patients must have failed at least 2 standard synthetic DMARDs and have at least 3 tender and 3 swollen joints.

Although it appears from indirect comparisons that efficacy in PsA may be lower than that for the TNF inhibitors, it should be noted that the efficacy on skin psoriasis is superior to that of TNF inhibitors and in dermatology registries, survival on ustekinumab is typically longer than that on TNF inhibitors.

Ustekinumab is given as a subcutaneous injection of 45 or 90mg. The standard dose for PsA is 45mg given at week 0, 4 and then every 12 weeks thereafter. However in patients weighing over 100kg, a higher 90mg dose should be used. Response for NICE using the PsARC should be assessed after 24 weeks of therapy.

7.7 Apremilast

Apremilast is an oral phosphodiesterase 4 inhibitor that is considered as a targeted synthetic DMARD or small molecule drug. It has proven efficacy in a number of clinical trials in PsA. Its efficacy appears to be similar to traditional synthetic DMARDs but with efficacy in multiple domains of PsA including peripheral arthritis, skin, enthesitis and dactylitis. The safety signal of apremilast has been very reassuring with no requirement for routine safety blood monitoring and no increased risk of infection, TB, demyelination, malignancies, cardiovascular events or vasculitis. It does however cause diarrhoea relatively frequently particularly in the early weeks after starting and has also been associated with weight loss in 10% of individuals.

Apremilast is prescribed orally at a dose of 30mg twice daily following an initial titrating dose over the first five days of administration (see below). Response for NICE using the PsARC should be assessed after 16 weeks of therapy.

Day 1		Day 2		Day 3		Day 4		Day 5		Day 6+	
AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
10mg	None	10mg	10mg	10mg	20mg	20mg	20mg	20mg	30mg	30mg	30mg

7.8 Secukinumab (or Ixekizumab)

Secukinumab is a humanised IL17A inhibitor recently licensed for the treatment of psoriatic arthritis. Its efficacy in peripheral arthritis appears similar to that for TNF inhibitors but it has been shown to have superior efficacy to TNF inhibitors and to ustekinumab in the treatment of skin psoriasis. Thus it may be a very useful therapy where rapid control of significant skin disease is required. Whilst response rates are lower in patients who have previously failed a TNF inhibitor, it still have significant efficacy compared to placebo particularly at the higher 300mg dose.

Secukinumab is prescribed as a subcutaneous injection at a dose of 150 or 300mg. The standard dose for PsA is 150mg given at week 0, 1, 2, 3 and 4 and then every 4 weeks thereafter. However in certain subpopulations the higher 300mg dose should be used: patients with significant skin psoriasis; patients with previous failure of a TNF inhibitor. Response for NICE using the PsARC should be assessed after 16 weeks of therapy.