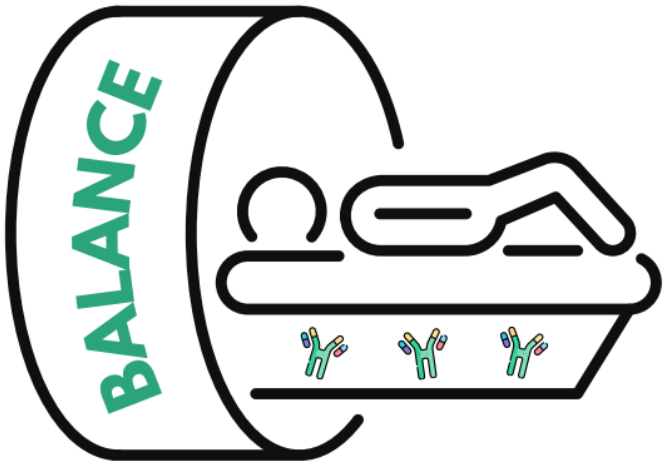
CLINICAL TRIAL PROTOCOL

This protocol has regard for the HRA guidance.



FULL TRIAL TITLE: A pilot mechanistic study to investigate the impact of Bimekizumab on liver inflammation in psoriatic disease

SHORT TRIAL TITLE: Bimekizumab And Liver inflAmmation in psoriatic disease: a pioNeering Clinical invEstigation

TRIAL ACRONYM: BALANCE

Version: 1.0 16-Mar-2026

Contents

1 RESEARCH REFERENCE NUMBERS

Sponsor Protocol Number:	PID19606
Clinical Trials Unit (CTU) Reference:	OCTRU449
Funder Reference(s):	UCB IIS-2024-600472
Ethics Reference Number:	XXXXX
IRAS Number:	340351
Registry:	International Standard Randomised Controlled Trial Number (ISRCTN): insert ISRCTN number here. URL to registry record: add link to registry record here Date of registration: add date of registration here
CPMS ID:	60927

2 ORGANISATIONAL INFORMATION

Chief Investigator (CI):	**Prof Laura Coates** NDORMS, University of Oxford Refer to the KEY TRIAL CONTACTS section for contact details.
Sponsor:	University of Oxford Refer to the KEY TRIAL CONTACTS section for contact details.
Clinical Trials Unit:	The trial is coordinated by the Experimental Medicine and Rheumatology group, part of the following UK Clinical Research Collaboration (UKCRC) registered Clinical Trials Unit (CTU). UKCRC Registered Clinical Trials Unit: Oxford Clinical Trials Research Unit (OCTRU) Botnar Research Centre, University of Oxford, Windmill Road, Headington, Oxford, OX3 7LF.
Funder:	The trial is funded by UCB. Refer to Funding and support in kind sub-section for full details of all funding sources.
Co-applicants on the trial grant:	The following are co-applicants on the trial grant and have contributed to the trial design and development of the protocol: **Dr Jennifer Williams** Senior Clinical Research Manager OCTRU, NDORMS, University of Oxford ✉ Jennifer.williams@kennedy.ox.ac.uk **Dr Sofia Massa** OCTRU Lead Statistician OCTRU, NDORMS, University of Oxford ✉ Sofia.massa@ndorms.ox.ac.uk **PATIENT AND PUBLIC CONTRIBUTORS** Not applicable
Additional protocol contributors:	**Dr Anne Francis** Operational Lead, Experimental Medicine and Rheumatology ✉ anne.francis@ndorms.ox.ac.uk **Mimi Bogale** Clinical Trial Manager OCTRU, NDORMS, University of Oxford ✉ balance@ndorms.ox.ac.uk

Conflict of Interest statement:	The following conflicts of interest have been declared by the co-applicants/protocol contributors: The Chief Investigator (CI) Prof Laura Coates has received grants/research support from Abbvie, Amgen, Janssen and UCB; worked as a paid consultant for AbbVie, Amgen, Bristol Myers Squibb, Eli Lilly, Enlivex, Janssen, Moonlake, Novartis, Pfizer, Takeda and UCB; and has been paid as a speaker for AbbVie, Amgen, Eli Lilly, Janssen, Novartis, Pfizer and UCB. **Management of Conflict of Interest:** The CI has declared a potential conflict of interest and is also the Principal Investigator (PI) at one research site. Measures are in place to ensure that this does not affect participant safety, study conduct, or data integrity. This is an observational cohort study. Treatments are prescribed as part of routine clinical care and are not allocated by the study. Medication is self-administered by participants in accordance with usual care. The CI does not administer interventions as part of the research. Participant recruitment and informed consent are conducted in accordance with Good Clinical Practice and the approved protocol. Eligibility is confirmed using predefined criteria, and consent will be received by appropriately trained delegated staff. Recruitment processes are subject to routine monitoring. Independent oversight is provided by a Trial Oversight Committee (TOC), which performs the functions of a Trial Steering Committee and Data and Safety Monitoring Committee. The TOC reviews study conduct and safety data and may recommend modifications if required. Data collection and analysis will follow a pre-specified statistical analysis plan finalised prior to database lock. The CI does not have sole control over the dataset or the analytical process.
Confidentiality:	The protocol will be published and made freely and openly accessible to all.

3 KEY TRIAL CONTACTS

Central CTU trial team /Coordinating centre for general queries	BALANCE trial team EMR, OCTRU, NDORMS, University of Oxford, Botnar Institute for Musculoskeletal Sciences, Windmill Road, Headington, Oxford, OX3 7LD ☎ 01865 613476 ✉ BALANCE@ndorms.ox.ac.uk
Chief Investigator (CI)	Laura Coates Associate Professor NDORMS, University of Oxford, Botnar Institute for Musculoskeletal Sciences, Windmill Road, Headington, Oxford, OX3 7LD ☎ 01865 737838 ✉ laura.coates@ndorms.ox.ac.uk
Sponsor:	University of Oxford Research Governance, Ethics & Assurance Team (RGEA) Boundary Brook House Churchill Drive Headington Oxford OX3 7GB ✉ RGEA.Sponsor@admin.ox.ac.uk
Lead Trial Statistician	Dr Sofia Massa OCTRU Botnar Research Centre Nuffield Department of Orthopaedics, Rheumatology & Musculoskeletal Sciences University of Oxford Windmill Road Oxford OX3 7LD ✉ sofia.massa@ndorms.ox.ac.uk ✉ octru-stats@ndorms.ox.ac.uk
Trial Oversight Committee (TOC) Chair:	Dr Alessandra Nerviani Experimental Medicine and Rheumatology William Harvey Research Institute Queen Mary University of London ✉ a.nerviani@qmul.ac.uk Other members of the TOC are detailed within a trial specific TOC charter.
Data and Safety Monitoring Committee (DSMC) Chair:	There is no DSMC for this trial. The TOC will cover both roles.

4 PROTOCOL APPROVAL/SIGNATORIES

This protocol has been approved by the Sponsor, Chief Investigator and Lead Trial Statistician. Approval of the protocol is documented in accordance with OCTRU Standard Operating Procedures (SOPs).

All parties confirm that findings of the trial will be made publicly available through publication without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any important deviations and serious breaches of Good Clinical Practice (GCP) from the trial as planned in this protocol will be explained.

5 LAY SUMMARY/PLAIN ENGLISH SUMMARY

In a previous trial we led, we discovered that liver disease, specifically non-alcoholic liver disease is common in patients with psoriatic disease (psoriasis or psoriatic arthritis). This risk or presence of liver disease can make it challenging for doctors as some therapies for psoriatic disease may worsen liver disease. However, there is some evidence that some of the newer medications used to treat psoriatic disease may actually improve liver health.

As liver disease can have a significant impact on an individual's health and quality of life, doctors want to study the livers of individuals who start to take one of the newer but licensed drugs for psoriatic disease called Bimekizumab and see any effects it causes on the liver. This can be achieved by using an MRI scanner which can be used alongside some computer software to look and measure any inflammation and scarring in the liver and other organs and this study will look at this at 2 time points – before starting Bimekizumab and then 6 months (24 weeks) later.

6 TRIAL SYNOPSIS

Full Trial Title:	A pilot mechanistic study to investigate the impact of Bimekizumab on liver inflammation in psoriatic disease
Short Title:	Bimekizumab And Liver inflAmmation in psoriatic disease: a pioNeering Clinical invEstigation
Trial Acronym:	BALANCE
Trial Design:	The BALANCE trial is a multi-centre, single-arm, observational cohort prospective clinical study.
Trial Aim/Primary Objective:	The aim of the trial is to explore the impact of Bimekizumab (IL17A&F inhibitor) on non-invasive measures of liver disease and links to underlying pathological mechanisms.
Trial Participants/ Target Population:	The BALANCE trial will recruit adults aged 18 years and over with psoriasis or psoriatic arthritis who are starting treatment with Bimekizumab. Refer to section 0 of the main body of the protocol for full eligibility criteria.
No. of trial arms:	One
Planned Sample Size:	30 participants
Target no. of research sites:	Up to 5 research sites
Countries of recruitment:	UK
Planned start date of recruitment:	Recruitment is planned to start in May 2026
Planned recruitment duration:	Recruitment is expected to last for 12 months
Duration of involvement:	Participants will be followed up in the trial for 24 weeks after they start treatment with Bimekizumab. The total trial duration may be longer given the delays in initiating treatment within National Health Service (NHS) procedures.

	Objective	**Outcome Measure**
Primary objective and outcome measure:	Change in liver inflammation and fibrosis following treatment with Bimekizumab	Liver cT1 level and Liver proton density fat fraction (PDFF) from CoverScan™ pre-treatment and 24 weeks post-treatment scans
Additional objectives and outcome measures:	Refer to the OBJECTIVES AND OUTCOME MEASURES section of the main body of the protocol for full trial objectives and outcome measures.	
Individual participant data (IPD) sharing statement:	The datasets generated during and/or analysed during the current trial will be available upon request from the lead trial statistician/ Chief Investigator. Refer to the KEY TRIAL CONTACTS section for contact details.	

7 ABBREVIATIONS

AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BASDAI	Bath Ankylosing Spondylitis disease activity index
BMI	Body mass index
BSA	Body surface area
CASPAR	Classification Criteria for Psoriatic Arthritis
CI	Chief Investigator
CRF	Case Report Form
CRP	C- reactive protein
CTU	Clinical Trials Unit
cT1	Corrected T1
CyTOF	Cytometry by Time-Of-Flight
DAPSA	Disease Activity Index for Psoriatic Arthritis
DICOM	Digital Imaging and Communications in Medicine
DLQI	Dermatology life quality index
DMARD	Disease modifying anti-rheumatic drug
DSMC	Data and Safety Monitoring Committee
ELF	Enhanced liver fibrosis (test)
EMR	Experimental Medicine and Rheumatology
FACS	Fluorescence- activated cell sorting
FBC	Full blood count
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Glucagon-like peptides
GP	General Practitioner
HAQ	Health assessment questionnaire
HCRW	Health and Care Research Wales
HRA	Health Research Authority
HTA	Human Tissue Act
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IL-17	Interleukin-17
IL-17i	Interleukin 17 inhibitor
IMD	Index of Multiple Deprivation
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
LEI	Leeds enthesitis index
LFT	Liver function test
MAIT	Mucosal-associated invariant T cells
MASLD	Metabolic dysfunction-associated steatotic liver disease
MRI	Magnetic resonance imaging
MTX	Methotrexate
NAFLD	Non-alcoholic fatty liver disease
NHS	National Health Service
NPC	Non-psoriatic control
OCTRU	Oxford Clinical Trials Research Unit
PASI	Psoriasis area severity index

PBMCs	Peripheral blood mononuclear cells
PDFF	Proton density fat fraction
PI	Principal Investigator
PICs	Participant identification centres
PID	Personal identifiable data
PIS	Participant Information sheet
PPI	Patient and Public Involvement
PsA	Psoriatic arthritis
PSAID	PsA impact of disease
PsO	Psoriasis
QA	Quality Assurance
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
RGEA	Research Governance, Ethics & Assurance
RNA	Ribonucleic acid
rRNA	Ribosomal Ribonucleic acid
SAE	Serious Adverse Event
SAR	Serious adverse reaction
SF-36	36-Item Short Form Survey
SJC	Swollen Joint Count
SFQ	Site feasibility questionnaire
SmPC	Summary of product characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Response/Reaction
TNF	Tumour necrosis factor
TJC	Tender Joint Count
TMF	Trial Master File
TMG	Trial Management Group
TOC	Trial Oversight Committee
UKCA	UK Conformity Assessed
UKCRC	UK Clinical Research Collaboration
UK GDPR	UK General Data Protection Regulation
ULN	Upper limit of normal
VAS	Visual analogue scale

8 BACKGROUND INFORMATION AND RATIONALE

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD) has been reported in 17-64% of patients with psoriatic disease[1,2]. Here NAFLD is used, as the literature review included here refers to earlier studies where this definition was used. Meta-analysis of 267,761 people indicated that the risk of NAFLD is significantly greater in psoriatic patients compared to non-psoriatic controls (NPCs), and that the risk is even greater in patients with psoriatic arthritis (PsA) or with moderate to severe psoriasis (PsO). The cause of the excess liver disease in PsO and PsA is not fully understood, but is likely to be a complex interplay of multiple related factors.

Methotrexate (MTX), standard of care for PsA, is associated with a dose dependent risk of acute hepatotoxicity, but also patients with NAFLD are at increased risk for MTX hepatotoxicity. Co-prevalence of psoriatic disease and NALFD substantially increase the severity of both diseases[3].

Metabolic syndrome (the name for a group of health problems that put individuals at risk of type 2 diabetes or other conditions that affect an individual's heart or blood vessels) is also a key driver of NAFLD. The prevalence of metabolic syndrome among patients with PsO is high (>30% among those beyond the age of 40 years) and 80% of PsA patients are overweight. During NAFLD, a change in the microbiota may lead to a reduction of endogenous folate production by limiting the pool of folate-producing lactobacilli and bifidobacteria. MTX would be expected to exacerbate this.

While the aetiology is clearly complex, the presence of systemic inflammation (as measured by liver-derived C-reactive protein), is a unifying feature that exacerbates all these mechanisms of liver injury. Psoriatic skin inflammation is not confined to the lesional site, as high levels of cytokines (Interleukin-17A (IL-17A), IL-17F, Tumour necrosis factor- α (TNF-α), IL-21, IL-22, and IL-26) and activated immune cells circulate to distant uninvolved skin, and other tissues or organs[4]. This association between remote sites of inflammation is highlighted by the dose-dependent relationship between improvement in psoriasis skin disease severity and in aortic vascular inflammation[5]. The PsA inflammatory cascade is less well understood but also includes IL-17A, IL-17F and IL-22 with a key pathological role played by CD8 T cells[6].

A fundamental challenge in managing and monitoring chronic liver disease in psoriatic patients is that they are asymptomatic in the early stages of their disease. Circulating biomarkers of liver damage such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) correlate poorly with the extent of liver involvement. Biopsy, which is currently the gold standard for assessing liver disease, is invasive, relatively risky, costly and evaluates only a small fraction (1/50,000th) of the liver[7]. A new technique for quantifying liver disease is urgently needed.

LiverMultiScan is a novel, CE-marked and Food and Drug Administration (FDA) cleared product developed by Perspectum (Perspectum Ltd, UK https://perspectum.com/) that can non-invasively quantify liver tissue characteristics based on magnetic resonance imaging (MRI). The uniqueness of this approach lies in the development of proprietary algorithms that can correct MRI parameters used in the assessment of tissue inflammation for the effect of liver iron content [corrected T1 (cT1) utilising 2 MRI measurements, T1 relaxation time and T2 relaxation time] [8].

The resulting proprietary cT1 technology has been shown to correlate with liver inflammation and fibrosis[8], predict clinical outcomes[9] and stage NAFLD/Non-alcoholic steato-hepatitis[10]. cT1 is complemented by the quantification of Proton Density Fat Fraction (PDFF) and accurately reflects the severity of liver disease[11]. The heterogeneity of liver disease is accounted for by computing values from multiple regions obtained from at least one liver image and by assessment of cT1 across an entire

cross-sectional slice of the liver. The accuracy and reproducibility of LiverMultiScan for all types of patients (such as people with obesity and high liver iron levels) is supported by data from clinical trials in liver disease cohorts, ranging from comparative studies that include healthy controls, to whole-population studies in the UK and US[8-14]. Sensitivity and specificity are high: LiverMultiScan has an "area under the curve" of 0.94 for the diagnosis of any stage of liver fibrosis, of 0.84 for any stage of ballooning (liver cell apoptosis) and of 0.93 for NAFLD[8]. Ongoing drug efficacy trials utilising LiverMultiScan show that the method can reliably detect significant changes in liver disease characteristics in less than 26 weeks [15] proving the exciting utility and responsiveness of this technique in longitudinal treatment studies.

Within the COLIPSO study (IIS-2021-146962 with co-funding from National Psoriasis Foundation), we are investigating the prevalence of liver disease in those with psoriatic disease (PsA and PsO). Analysis has shown a significantly increased prevalence of liver disease compared to age, sex and Body Mass Index (BMI) matched NPC data from the UK Biobank.[16] In the psoriatic cohort (33 patients analysed so far), the mean age was 50 years, and the majority were overweight or obese (77%) with a mean BMI of 29 kg/m^2. The psoriatic group had significantly higher prevalence of abnormally elevated liver cT1 at two thresholds (≥800ms) and (≥875ms) compared to NPCs (33% vs 14%, p = 0.022 and 21% vs 2%, p = 0.002 respectively). Despite this, prevalence of elevated liver fat (PDFF ≥5%) was not significantly different between psoriatic cases and NPCs (52% vs 36%, p = 0.146). We expect a similar proportion of the BALANCE trial cohort to have liver disease as they should be a comparable population.

In the BALANCE trial, the liver will be assessed by the CoverScan™ MRI protocol another CE-marked and FDA 510(k)-cleared product developed by Perspectum. CoverScan™ measures the same liver metrics as LiverMultiScan (cT1 and PDFF) but also measures tissue steatosis, fibro inflammation and function in heart, lungs, kidneys, pancreas and spleen allowing assessment of multi-organ disease in the cohort of psoriatic disease participants.

The role of gut dysbiosis in psoriatic disease is becoming more evident[17] but the potential impact of this dysbiosis on the liver, which is the first site of processing for microbial metabolites, has not yet been investigated. In particular, the liver contains a population of resident mucosal-associated invariant T cells (MAIT) which recognise microbial metabolites[18] and are capable of producing pro-inflammatory type 17 cytokines such as IL-17A[19] and IL-17F[20], an established therapeutic target in psoriatic disease[21-23]. MAIT cells have been associated with the pathogenesis of psoriatic disease[24,25] and thus uniquely poised to link gut dysbiosis with Th17-driven joint inflammation.

Within the COLIPSO trial, we have identified a preliminary signal supporting the impact of IL-17 therapies. To date, follow up data are available on 21 people, 6 months after switching to a new Disease Modifying Anti-Rheumatic Drug (DMARD). Of these, patients who switched to MTX (n=9) showed possible signs of deterioration in cT1 as compared to all other treatments (mean change +52ms [95%CI -7ms to +110ms] vs -12ms [95%CI -50ms to 27ms], p = 0.041). In contrast, patients switching to IL-17 therapies (Secukinumab or Ixekizumab, n=4) showed mean absolute improvements in PDFF (-1.9% [95%CI -4.6% to +0.8%] vs +1.3% [95%CI -0.3% vs 2.9%], p = 0.025) and mean cT1 (-59ms [95%CI -132ms to +14ms] vs +33ms [95%CI -2ms to +68ms], p = 0.018), but no difference in serum biomarkers (ALT and AST). A similar improvement was not seen with other non-IL-17 inhibitor biologics such as TNF inhibitors. A small subset of patients in COLIPSO also underwent CoverScan™ MRI protocol to allow preliminary investigation of inflammation and fibrosis in other organs in people with psoriatic disease.

9 OBJECTIVES AND OUTCOME MEASURES

9.1 Aim

The aim of the trial is to explore the impact of Bimekizumab (IL17A&F inhibitor) on non-invasive measures of liver disease and links to underlying pathological mechanisms.

9.2 Primary objective and outcome measure

The primary objective and outcome measure are defined in Table 1.

Table 1: Details of primary objective

Objective	Outcome measure	Time point(s) of evaluation of this outcome measure (if applicable)	Data required	Source data (including location)
To define the effect of dual IL17A&F inhibition with Bimekizumab on liver inflammation and fibrosis in psoriatic disease	Liver cT1 level and Liver proton density fat fraction (PDFF)	Pre-treatment and 24 weeks post-treatment	MRI images analysed and median Liver cT1(ms) with interquartile range (IQR) and median Liver Fat (%, PDFF) with IQR derived and provided by Perspectum	MRI scans obtained using the CoverScan™ MRI protocol.

9.3 Secondary objectives and outcome measures

The secondary objective/s and outcome measure are defined in Table 2.

Table 2: Details of secondary objectives

Objective	Outcome measure	Time point(s) of evaluation of this outcome measure (if applicable)	Data required	Source data (including location)
To define the effect of dual IL17A&F inhibition with Bimekizumab on other organ inflammation and fibrosis in psoriatic disease	MRI biomarkers of fibro-inflammation in heart, lungs, kidneys, pancreas and spleen	Pre-treatment and 24 weeks post-treatment	MRI images analysed and scores derived and provided by Perspectum **Heart**: left and right ventricular heart ejection fraction (%) Cardiac T1 and T2 levels (ms) Ascending Aorta Diameter (mm) Abdominal Aorta Diameter (mm) **Kidney**: left and right median kidney cortical T1 levels (ms) left and right kidney length (cm) **Lungs**: left and right median fractional changes (%) **Pancreas**: median pancreatic srT1 level (ms) and median pancreas fat fraction (%, PDFF) **Spleen**: spleen length (cm) Visceral fat area (cm^2) Subcutaneous fat area (cm^2) Skeletal muscle area (cm^2) Psoas muscle area (cm^2)	MRI scans obtained using the CoverScan™ MRI protocol.
To explore whether organ inflammation and fibrosis is similar in those with PsO and PsA	Liver cT1 level and Liver Proton Density Fat Fraction (PDFF)	Pre-treatment and 24 weeks post-treatment	MRI images analysed and scores derived and provided by Perspectum **Liver:** Liver cT1 level and Liver Proton Density Fat Fraction (PDFF)	MRI scans obtained using the CoverScan™ MRI protocol.

Objective	Outcome measure	Time point(s) of evaluation of this outcome measure (if applicable)	Data required	Source data (including location)
	MRI biomarkers of fibro-inflammation in heart, lungs, kidneys, pancreas and spleen		**Heart**: left and right ventricular heart ejection fraction (%) Cardiac T1 and T2 levels (ms) Ascending Aorta Diameter (mm) Abdominal Aorta Diameter (mm) **Kidney**: left and right median kidney cortical T1 levels (ms) left and right kidney length (cm) **Lungs**: left and right median fractional changes (%) **Pancreas**: median pancreatic srT1 level (ms) and median pancreas fat fraction (%, PDFF) **Spleen**: spleen length (cm) Visceral fat area (cm^2) Subcutaneous fat area (cm^2) Skeletal muscle area (cm^2) Psoas muscle area (cm^2)	
To explore if liver disease is associated with disease activity in PsO and PsA	Liver cT1 level and Liver Proton Density Fat Fraction (PDFF) Disease activity measures (PASI scores, DAPSA scores, Dactylitis, Enthesitis, BSA)	Pre-treatment and 24 weeks post-treatment	MRI scores derived and provided by Perspectum PASI scores: Erythema, scaling, Induration, Extent of involvement in head, upper limbs, trunk and lower limbs. DAPSA scores: TJC, SJC, Patient Pain VAS, Patient Global VAS, CRP LEI, Dactylitis count, BSA	MRI scans obtained using the CoverScan™ MRI protocol. Clinical data from REDCap and patient reported questionnaires

Objective	Outcome measure	Time point(s) of evaluation of this outcome measure (if applicable)	Data required	Source data (including location)
To explore if other organ inflammation/fibrosis is associated with disease activity in PsO and PsA	MRI biomarkers of fibro-inflammation in heart, lungs, kidneys, pancreas and spleen Disease activity measures (PASI scores, DAPSA scores)	Pre-treatment and 24 weeks post-treatment	MRI images analysed and scores derived and provided by Perspectum **Heart**: left and right ventricular heart ejection fraction (%) Cardiac T1 and T2 levels (ms) Ascending Aorta Diameter (mm) Abdominal Aorta Diameter (mm) **Kidney**: left and right median kidney cortical T1 levels (ms); left and right kidney length(cm) **Lungs**: left and right median fractional changes (%) **Pancreas**: median pancreatic srT1 level (ms) and median pancreas fat fraction (%, PDFF) **Spleen**: spleen length (cm) Visceral fat area (cm^2) Subcutaneous fat area (cm^2) Skeletal muscle area (cm^2) Psoas muscle area (cm^2) DAPSA scores: TJC, SJC, Patient Pain VAS, Patient Global VAS, CRP LEI, Dactylitis count, BSA	MRI scans obtained using the CoverScan™ MRI protocol. Clinical data from REDCap and patient reported questionnaires
To explore the response after treatment with IL17A&F inhibition (Bimekizumab) via patient reported outcomes in psoriatic disease	Change in patient reported outcomes	Pre-treatment and 24 weeks post-treatment	SF-36, DLQI (PsO only), HAQ (PsA only), BASDAI (PsA and axial disease only), PsAID (PsA only), spinal Pain VAS (PsA and axial disease only)	Data from patient reported questionnaires

9.4 Exploratory objectives/additional mechanistic objectives outcomes

Exploratory/mechanistic objectives and outcome measure are defined in Table 3.

Table 3: Details of exploratory/mechanistic objectives

Objective	Outcome measure	Time point(s) of evaluation of this outcome measure (if applicable)	Data required	Source data (including location)
To explore the cellular drivers of inflammation in psoriatic disease	Different circulating cell types including MAIT cells, Th17 and key immune cells	Pre-treatment and 24 weeks post-treatment	Measured levels and proportions of cell types using flow cytometry	Laboratory records
To explore the soluble mediators of inflammation in psoriatic disease	Circulating inflammatory proteins and cytokines	Pre-treatment and 24 weeks post-treatment	Cytokine levels measured in serum/plasma	Laboratory records
To explore the microbiome genomic contributors to inflammation in psoriatic disease	Microbiome Ribonucleic acid (RNA) sequencing from stool sample and sequencing from peripheral blood Diet questionnaire	Pre-treatment and 24 weeks post-treatment	Sequencing data from peripheral blood and stool samples, Diet questionnaire	Laboratory records Patient-reported diet questionnaire

9.5 Choice of primary outcome

The primary outcome is the objective measurement of inflammation and fibrosis of the liver as measured using cT1 level and PDFF scores from the CoverScan™ MRI protocol[8]. This is a validated measure of liver disease.[8-10,26]

9.6 Use of core outcome sets (COS)

Core outcome sets for psoriatic disease are being addressed in this trial with regard to clinical and patient-reported outcome measures.[27]

10 TRIAL DESIGN AND SETTING

The BALANCE trial is a multi-centre, observational cohort prospective clinical study.

The trial will recruit 30 patients with PsO or PsA from approximately five sites in the UK. Participants will be about to start Bimekizumab as part of their standard care.

Participant timeline (see APPENDIX 1 – TRIAL FLOW CHART).

- **Screening**
  - Visit 1 – Clinic Visit: eligibility assessment, consent process, pre-treatment outcomes recorded and pre-treatment samples taken. Participants will be provided with a stool sample collection kit and diet questionnaire to complete at home and return in pre-paid packaging to the central laboratory.
  - Registration to the trial (no visit required): standard of care blood tests will be reviewed to confirm eligibility to start Bimekizumab either at Visit 1 (if results from previous routine blood tests done within the last month are available and suitable for use) or following Visit 1 (prior to Visit 2)
- **Pre-treatment**
  - Visit 2 – Pre-treatment MRI Scan (can be combined with Visit 1 if prior standard of care blood tests are available for review at Visit 1)
- **Baseline**
  - Day 0 – the start date of Bimekizumab therapy. No visit required.
- **24-Week Follow-up**
  - Visit 3 – Clinic Visit (+/- 2 weeks): post-treatment outcomes recorded and post-treatment samples taken. Participants will be provided with a stool sample collection kit and diet questionnaire to complete at home and return in pre-paid packaging to the central laboratory.
  - Visit 4 – 24- Week MRI Scan (+/- 2 weeks) – can be combined with Visit 3

Clinic visits (Visits 1 & 3) may align with routine standard care clinic visits.

10.1 Recruiting sites/site types

Participants will be recruited from dermatology and rheumatology departments from approximately five NHS secondary care hospitals who see adults with PsO or PsA.

Refer to section 29 for information on identification and management of participating sites.

10.1.1 Participant Identification Centres (PICs)

PICs are not used in this trial.

10.2 Collection of outcome data and follow-up assessments

All participants will receive a multiparametric MRI scan pre-treatment (or up to 1 week after starting Bimekizumab) and at 24 weeks (+/-2 weeks) so that measurements of cT1 and PDFF can be assessed before and after initiation of treatment. Composite clinical outcome measurements including clinician-assessed and patient-reported outcome measures will be collected in clinical visits at the hospital with the option to complete patient-reported outcomes at home following the screening visit or ahead of the follow-up visit. Blood samples will be collected at the clinic visits; stool samples will be provided at home following the clinic visits and sent directly to the central laboratory.

Refer to section 17.2 for full details of outcome data collection and follow-up assessments.

10.3 Countries of recruitment

UK

10.4 Duration of participant involvement

Participants will be in the trial for approximately 8 months from start of screening to last protocol visit (to account for any NHS processes in initiating treatment) including a 24-week period on Bimekizumab.

10.5 Post-trial treatment/care and follow-up

Following a participant's final protocol visit, they will receive standard care. As all participants will be receiving Bimekizumab as part of standard care, they will be able to continue this treatment as long as clinical response is satisfactory (as per standard NHS care and this is not assessed as part of this trial).

10.6 Central review procedures

MRI reports including analysis on the different organs will be compiled by Perspectum. This will include a safety review to identify any undiagnosed concerning clinical feature that will be reported back to the PI at the site as soon as possible after each MRI scan to allow any further investigations as planned. No MRI reporting is required from the participating sites.

10.7 Use of clinical registries and national datasets (e.g. NHS England)

No data of this type is to be accessed for this trial.

10.8 Expected recruitment rate

The anticipated monthly recruitment rate is 2-3 participants per month. Each of the 10 departments in the trial (dermatology and rheumatology departments in each of 5 hospitals) planned to take part in the BALANCE trial currently provide care for ~2000 patients with PsO or PsA. It has been conservatively estimated that 50% of eligible patients will consent to take part in the trial. Therefore, each site is expected to recruit an average of 0.5-1 participant per site/per month. It is expected that all sites will be open within 3 months of recruitment starting.

10.9 Equality, diversity and inclusion for trial participants

The Index of Multiple Deprivation (IMD) will be collected at screening for all consented trial participants in the UK to inform assessment of inclusivity regarding social deprivation. Staff recording pre-treatment data will be provided with a link to a web-based IMD Decile Lookup tool (managed by OCTRU) to obtain an individual's IMD decile group. Site staff will record the IMD decile on the IMD Case Report Form (CRF) within the Research Electronic Data Capture (REDCap) data collection system. Ethnicity data will be self-reported by participants via REDCap, using standard UK national classification categories.

While patient-reported questionnaires will be offered electronically, the option to complete these on paper with support at the visits will be made available.

10.10 End of trial

The end of trial is the point at which all the data (including analysis of all samples collected during the trial) has been collected, all queries resolved and all data derived from the MRI scans has been generated by Perspectum and received at the CTU.

The trial will stop recruiting participants once 30 participants have been registered, completed their pre-treatment MRI and have started Bimekizumab treatment.

The Sponsor and the Chief Investigator (CI) reserve the right to terminate the trial earlier at any time. In terminating the trial, they must ensure that adequate consideration is given to the protection of the participants' best interests.

11 SCREENING AND PARTICIPANT ELIGIBILITY CRITERIA

Participant eligibility will be confirmed by a suitably qualified and experienced individual who has been trained on the trial and delegated to do so by the PI.

11.1 Overall description of trial participants

The BALANCE trial will recruit adults aged 18 years or over with PsO or PsA who are starting treatment with Bimekizumab.

11.2 Inclusion Criteria

A patient will be eligible for inclusion in this trial if **ALL** of the following criteria apply:

- Aged 18 years or over
- Confirmed diagnosis of Psoriasis or Psoriatic Arthritis and are eligible and due to start systemic treatment with Bimekizumab as part of routine NHS care
- Willing and able to give informed consent

11.3 Exclusion Criteria

A patient with not be eligible for the trial if **ANY** of the following apply:

- Any contraindication to magnetic resonance imaging (MRI) (including pregnancy, extensive tattoos, pacemaker, shrapnel injury, severe claustrophobia) or any other disorder which may put the participant at risk
- Previous IL-17 inhibitor therapy for any indication
- Regular alcohol intake of >28 units/week and/or a history of binge drinking
- Patients with known or suspected autoimmune hepatitis, viral hepatitis or Wilson's disease
- Participating or planning to participate in another interventional clinical study/trial during the study period that in the opinion of the investigator could affect BALANCE outcomes
- Any other cause, including a significant disease or disorder which, in the opinion of the investigator, may either put the participant at risk because of participation in the trial, or may influence the participant's ability to participate in the trial

11.4 Rationale for inclusion and exclusion criteria

The inclusion criteria require patients with a diagnosis of psoriatic disease who are eligible for treatment with Bimekizumab according to standard NHS requirements. The exclusion criteria ensure safety of the participants, ensuring that they are safe to receive the medication Bimekizumab and to undergo the MRI scanning. They also ensure that participants do not have significant other liver diseases that may impact on the results of the MRI scan.

11.5 Screening tests or investigations

There are no pre-trial screening tests for inclusion in the trial. Assessments performed as part of routine care will be used to screen patients for eligibility.

11.6 Timing of eligibility assessment

Eligibility to start Bimekizumab treatment requires review of the standard care blood tests taken at the screening visit therefore, eligibility for the trial will be assessed in two parts:

Eligibility Part 1: At the screening visit participants will be deemed potentially eligible if they have a confirmed diagnosis of PsO or PsA and are *planning* and due to start systemic treatment with

Bimekizumab as part of routine NHS care, meet the other inclusion criteria and do not meet any of the exclusion criteria.

Eligibility Part 2: Review of the standard care blood tests taken at the screening visit to confirm participants are *eligible* and due to start systemic treatment with Bimekizumab as part of routine NHS care before entry into the trial.

11.7 Re-screening if a potential participant does not meet inclusion/exclusion criteria at first assessment

Potential participants who fail at screening or who fail any other criteria at first assessment are ineligible and cannot be rescreened.

11.8 Use of screening logs

A screening log within the REDCap data collection system will be used to record information about the number of patients assessed for eligibility and/or approached for the trial and if provided, the reasons for exclusion or declined consent. Limited personal identifiable data (PID) such as sex and age band will be recorded on the screening log.

11.9 Duration between screening, registration and baseline

The duration between screening and registration (confirmation of eligibility part 2) will be approximately a week dependent on NHS laboratory turnaround time on standard care blood tests. The duration between screening and baseline will be approximately 3-6 weeks dependent on NHS timelines for prescribing and dispensing Bimekizumab which includes training on administration to be provided to the patient. These estimates could be longer if there are NHS delays in initiating treatment and will not require reporting as a protocol deviation.

11.10 Protocol waivers to entry criteria

Protocol adherence is a fundamental part of the conduct of a research trial. There will be no exceptions regarding eligibility (i.e. each participant must satisfy all the eligibility criteria). Changes to the approved inclusion and exclusion criteria may only be made by a substantial amendment to the protocol.

Before entering a patient onto the trial, the PI or designee will confirm eligibility. If unsure whether the potential participant satisfies all the entry criteria and to clarify matters of clinical discretion, investigators should contact the central CTU trial team, who will contact the CI or designated clinicians as necessary. If in any doubt, the CI must be consulted before recruiting the patient. Details of the query and outcome of the decision must be documented in the Investigator Site File (ISF) and Trial Master File (TMF).

11.11 Clinical queries and protocol clarifications

Every care has been taken in drafting this protocol. Contact the central CTU trial team for clarification if any instructions seem ambiguous, contradictory or impractical. Clinical queries must also be directed to the central CTU trial team. All clinical queries and clarification requests will be logged, assessed and a written response provided. Minor administrative corrections or clarifications will be communicated to all trial investigators for information as necessary. For urgent safety measures or changes that require protocol amendment see section 30.6.

12 ELIGIBILITY CRITERIA FOR SITES OR OTHER INDIVIDUALS INVOLVED IN TRIAL

Participating sites will ideally have the following capabilities or the ability to put them in place:

- Prior experience with Perspectum procedures, **or** willingness to complete required set-up and training before activation.
- Ability to collect and isolate Peripheral blood mononuclear cells (PBMCs) per the laboratory manual requirements.

13 RECRUITMENT

13.1 Participant Identification

Participants will be recruited from dermatology and rheumatology departments within NHS hospitals in the United Kingdom.

The following methods will be used to identify potentially eligible participants:

- Searching of clinic records/hospital databases by the usual care team to identify individuals that may be eligible to enter the trial.
- Identification during routine clinic visits by the usual care team.

13.1.1 Identification of participants via clinic records/hospital database

Potentially eligible patients will be identified by searching clinic records/hospital databases at participating research sites by those in the usual care team only. Any patients who are thought to fulfil the inclusion/exclusion criteria will be sent a letter of invitation by their usual care team on behalf of the site research team together with a Participant Information Sheet (PIS). For those patients that are potentially interested in learning more, they will be directed to contact the local site research team.

13.1.2 Identification of participants during routine clinic visits

Potentially eligible patients identified during routine clinic visits will be provided with a PIS by a member of their usual care team (who may also be a member of the site research team) and asked to consider the trial. Where their usual care clinician is not a member of the site research team, potential participants will be asked if it would be acceptable to meet a member of the site research team following their routine clinic visit or for their name and contact details to be passed to the site research team who will make contact at a later time point (this may be in person in a clinic or via telephone or video call in accordance with local site practice). Alternatively, potential participants may be given the PIS and asked to call the number on it if they wish to find out more about the trial. When a potential participant is approached for permission for their details to be passed onto the site research team – if this permission is given this must be recorded in their clinical notes.

14 TRIAL INTERVENTION AND COMPARATOR

This is not an interventional trial, but an observational cohort. Only patients starting Bimekizumab as part of their standard care treatment will be included.

15 INFORMED CONSENT

15.1 Consent Procedure

Informed consent will be collected and if a person approached is willing to give consent it will be collected by a member of the site research team delegated the responsibility of receiving consent before they undergo any trial-related procedures. A member of the site research team will explain the details of the trial in addition to the already presented PIS, ensuring that the potential participant has

sufficient time to consider participating or not. A member of the site research team will answer any questions that the potential participant has concerning trial participation.

15.2 Time allowed to decide to take part

Potential participants will have sufficient time to decide on whether to take part or not. If participants are happy, they will be able to consent at their routine clinic visit, providing this occurs prior to commencing Bimekizumab treatment and prior to the study recruitment end date

15.3 Completion of the Informed Consent Form (ICF)

The potential participant and the PI (or authorised designee) must personally sign and date the current approved version of the ICF before any trial specific procedures are performed.

The ICF will usually be offered to participants in clinic as an electronic form on a tablet device (with the consent form being filled in directly on REDCap), however paper consent forms will also be made available for use in situations where electronic consent is not possible or suitable.

Where consent forms are completed electronically, signatures will be either achieved by a finger tracing across a tablet device, using an electronic stylus on a tablet device or using a mouse dragging the cursor across the screen – all methods are to be used as if signing with a traditional pen.

Where electronic consent is used and the participant has an email address which they are willing to provide, an electronic version of the signed ICF will be automatically emailed to them. If the participant does not have/does not provide an email address the site research team will be able to print a copy of the signed ICF and provide this to the participant. A downloaded copy of the electronic consent must be placed in the ISF and a copy in the participant's medical record.

For participants who consent to their samples being used for future research, a copy of the signed consent form and related information sheet will be sent to the Oxford Musculoskeletal Biobank, to comply with the storage requirements of the Human Tissue Act (HTA), at the end of the trial.

15.4 Optional aspects of consent

Eligible individuals who agree to participate in the trial, will also be asked to give consent to the following optional aspects of the trial:

- Samples and linked clinical data (which will not identify the participant) to be used in future ethically approved research in the UK or abroad which may involve commercial organisations
- Storage of contact details in order to provide participant with summary of the findings at the end of the trial

Participation in these elements of the research is voluntary and refusal to participate will not affect their inclusion in the trial. Refusal to participate will involve no penalty or loss of benefits to which the individuals would otherwise be entitled or their standard management in any way.

15.5 Individuals lacking capacity to consent

Individuals lacking capacity to consent to trial participation will not be eligible to enter the trial.

15.6 General Practitioner (GP) notification

Participants will be made aware as part of the informed consent process that if they consent to take part in the trial their GP will be informed of their participation in the trial. An approved GP letter will be sent by the BALANCE site research team together with trial information to the participant's GP informing them of their participation in the trial. Participants will also be informed that, should the

MRI scans identify findings suggestive of liver disease, relevant information will be shared with their GP to support appropriate clinical follow-up.

15.7 Re-consenting

Should there be any subsequent amendment to the final protocol, that might affect a participant's participation in the trial, continuing consent will be obtained using an amended consent form which will be signed by the participant and the PI (or authorised designee).

15.8 Participants who lose capacity during the trial

Participants who consent and are included in the trial who lose capacity during the trial will be withdrawn and have their data available for use up until the point when they lose capacity. After this point ongoing consent is not valid.

16 REGISTRATION

16.1 Timing of registration

Registration will only be performed when informed consent has been received and the participant is deemed eligible to enter the trial.

16.2 Registration procedure

Registration into the trial can occur following review of the standard of care blood tests either taken at the screening visit or done within the last month to confirm eligibility to start Bimekizumab treatment. Registration will be remote and not require a trial visit.

17 TRIAL ASSESSMENTS/PROCEDURES AND DATA COLLECTION

The trial flow chart can be found in Appendix 1 of this protocol.

17.1 Trial Assessments

Table 4 shows scheduled assessments including required samples for the trial.

17.1.1 Screening

At screening, all participants will undergo eligibility assessment and consent process ahead of any trial procedures being conducted. After consent, participants will have medical history, concomitant medications recorded and IMD recorded, clinical assessments, complete patient reported outcome measures (or given the option to complete these electronically at home following the visit via a link) (see Table 5: REDCap Data Collection), have standard care blood samples collected (unless results from routine clinical care within the last month are available and suitable for use), have research blood samples taken and given a kit to collect a stool sample (with accompanying diet questionnaire) at home following the visit.

Medical History and concomitant medication (10 mins)

Relevant medical history and details of concomitant medication (PsA/PsO treatments and other chronic therapies such as antidiabetic agents, lipid-lowering medications, antihypertensives, and glucagon-like peptides/GLP receptor agonists) will be recorded.

Clinical Assessment (20 mins)

Clinical assessment will be tailored to the diagnosis of the participant (either PsO only or PsA). For all participants, we will collect height, weight, waist and hip circumference and Physician's assessment

of overall disease activity (per diagnosis). For those with skin psoriasis, an assessment of skin disease including Psoriasis Area Severity Index (PASI) and Body Surface Area (BSA) will be performed. For those with PsA, they will also have a Classification Criteria for Psoriatic Arthritis (CASPAR) criteria assessment, 68/66 tender/swollen joint count, enthesitis assessment using Leeds Enthesitis Index (LEI) and dactylitis count (0-20).

Blood sample (10 mins)

15 mL blood will be withdrawn for standard care blood tests which include full blood count (FBC), C-reactive protein (CRP) and liver function test (LFT) including Alanine Aminotransferase (ALT). 5 mL blood will be withdrawn for an ELF test[28] for research. An additional blood sample (~45 mL) will be withdrawn for additional research with 40 mL for plasma and 5 mL for serum.

Registration (5 mins)

Registration into trial can occur once standard care blood tests have been reviewed to confirm eligibility to start Bimekizumab. If standard care blood tests are taken at screening, the registration will usually be within a week after screening however if standard care blood tests results are available from a recent prior routine visit (in the last month) and eligibility to start Bimekizumab is confirmed, registration can occur on the same day as screening.

17.1.2 Pre-treatment MRI scan

Once registered onto the trial a multiparametric MRI scan (without contrast) will be arranged to allow measurements of cT1 level, liver PDFF and other MRI biomarkers of fibroinflammation in heart, lungs, kidneys, pancreas and spleen prior to Bimekizumab treatment. This may take place on the same day as the screening visit (if the participant is registered onto trial on the same day as screening) or may be a separate visit as required by MRI access at each site.

One research site will arrange for participants to undergo MRI scans at Perspectum's MRI facility. The remaining research sites will perform MRI scans locally within their NHS Trust in accordance with the study imaging requirements.

Arrangement of the MRI scan appointments at Perspectum will require sharing of the participant's full name, date of birth, and contact details (email address and telephone number) with Perspectum (supplier/ developer of the CoverScan™ MRI protocol). This is detailed in the PIS.

MRI Scan (~45 mins)

All participants will undergo a standardised imaging protocol in an MRI scanner and have their blood pressure, height and weight measured. Participants will be informed in the PIS that their images will be stored. The MRI scan is not painful or risky, but a small minority of people may feel claustrophobic. If this is apparent during Screening, patients will be advised to not participate. If this becomes apparent during a scan, the scan will be stopped and the participant taken out of the scanner. Wherever possible, the MRI scan will be conducted prior to the participant starting on Bimekizumab. In case of delays in MRI access, pre-treatment MRI scans will be permitted up to 7 days/ 1 week after the start Bimekizumab. It is unlikely that treatment with any disease-modifying drug will have significantly affected the results of the liver scan within this time period.

17.1.3 Baseline- first dose of Bimekizumab

No hospital visit is required. The site research team will confirm with each participant the date of their first Bimekizumab treatment. This can be conducted by telephone or remotely by email according to the participant's wishes. The Bimekizumab start date is 'Day 0' and the Week 24 follow-up visit will be timed from this date.

It is expected that the date of first dose of Bimekizumab will be 3-6 weeks after the screening visit due to Bimekizumab being prescribed and dispensed as part of NHS standard care which includes provision of Bimekizumab and training on administration to be provided to the patient.

Note: Bimekizumab is administered via subcutaneous injection, using a pre-filled syringe or auto-injector pen.

17.1.4 24-Week Follow-up

The 24-week clinic visit will be scheduled to take place 24 weeks after Baseline ('Day 0' start of Bimekizumab treatment) +/- 2 weeks.

All participants will undergo medical history and concomitant medications review, clinical assessments (same as at screening without CASPAR criteria), complete patient-reported outcome measures (or given the option to complete these electronically at home prior the visit via a link), have standard care blood samples collected, have research blood samples taken, given a kit to collect stool sample (with accompanying diet questionnaire) at home following the visit.

All participants will undergo a standardised imaging protocol in an MRI scanner and have their height, weight and blood pressure measured prior to the scan. The MRI scan can be arranged on the same day as the Week 24 Follow-up clinic visit or on a separate day (within the follow-up window) depending on which is most feasible for the site and participant.

Table 4: Schedule of assessments

	Assessment	Screening	Pre-treatment	Baseline – Day 0	24- Week Follow-up (+/- 2 weeks)
SITE RESEARCH TEAM	Patient approach, Informed consent	X			
	Confirm Eligibility	X			
	Registration	X			
	Medical History	X			X
	Concomitant medication check	X			X
	CRF completion (see 17.2 for details of data collected)	X	X[1]	X	X
	Completion of clinical assessments	X			X
RADIOLOGY/ PERSPECTUM	MRI scan		X[1]		X[2]
TREAT MENT	Bimekizumab treatment commenced			X	
PARTICIPANT COMPLETED	Participant-completed questionnaires/outcomes (see 17.2 for further details)	X			X
SAMPLES	Routine blood samples for C-Reactive Protein (CRP), FBC and LFT	X			X
	Research Blood samples	X			X
	Stool sample collection for microbiome analysis (taken at home and posted)	X			X
SAFETY	Safety reporting	X	X	X	X

[1] – Pre-treatment MRI scan may be performed on the same day as screening if standard care blood tests available for review. Can also be performed separately but must be performed within 7 days/1 week of starting treatment with Bimekizumab

[2] – 24- Week Follow-up MRI scan can be performed on same day as 24- Week Follow-up Clinic Visit or on a separate day (within the follow-up window) depending on which is most feasible for the site and participant.

17.2 Data Collection

Table 5: data collection

Data collected by site research team	Screening Visit	Pre-treatment	Baseline-Day 0	24-week visit (+/-2 weeks)
Height	X	X		X
Weight	X	X		X
Waist and Hip circumference	X			X
Concomitant medication use	X			X
Medical History (including alcohol intake)	X			X
IMD	X			
Physician's Visual analogue scale (VAS) of overall disease activity	X			X
Psoriasis Area Severity Index (PASI) and Body surface area (BSA)	X			X
PsA only • Classification Criteria for Psoriatic Arthritis (CASPAR) Criteria	X			
PsA only: • 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 enthesitis index	X			X
CRP/ELF measurements	X			X
FBC/LFT within normal range	X			X
Bimekizumab start date			X	
MRI scan		X		X
Data directly reported by participants (patient-reported outcomes)				
Ethnicity	X			
Participant pain VAS [1]	X			X
RAND 36-Item Short Form Survey (SF-36)	X			X

PsO only • Patient skin severity • DLQI	X			X
PsA only: • Patient Global Assessment (PGA) of disease activity • Health assessment questionnaire (HAQ) • PsA impact of disease (PSAID)	X			X
PsA where there is spinal involvement • Bath Ankylosing Spondylitis disease activity index (BASDAI) and spinal pain VAS	X			X
Diet questionnaire (including antibiotic use)	X			X

[1] For PsA participants- Participant pain VAS included in the HAQ

17.3 Procedure and method of trial questionnaire completion

Participants will be emailed a link to complete their trial questionnaires electronically where possible (participants will be asked at their screening visit whether they wish to complete questionnaires remotely or at their trial visit). Any links sent to a participant by email is unique to a participant and their timepoint/questionnaire in the trial. Questionnaires may also be completed on paper at the time of the trial visit where use of electronic means is not possible or suitable.

17.4 Communication with trial participants by the CTU trial team

Participants will be notified to complete trial questionnaires by email. Participants may be sent up to two reminder emails to complete questionnaires or will be asked to complete their questionnaire during their routine clinic visit.

17.5 Withdrawal and change to consent

Withdrawal of consent means that a participant has expressed a wish to withdraw from the trial altogether or from certain aspects of the trial only. The type of withdrawal will be collected on the Withdrawal CRF within REDCap.

Participants may also be withdrawn from the trial (or aspects of the trial) by their clinician if they believe the participant needs to be withdrawn.

Participants who do not complete their pre-treatment MRI scan and/or do not commence treatment with Bimekizumab will be withdrawn from the trial by the site Investigator (or designee).

The Withdrawal CRF must be completed to document the reasons for withdrawal and state who made the decision to withdraw. Discussions and decisions regarding withdrawal must be documented in the participant's medical notes. The PI (or delegate) must continue to follow up any Serious Adverse Events (SAEs) and continue to report any SAEs to resolution in the CRF in accordance with the safety reporting section of this protocol.

Where a participant expresses a wish to withdraw from the trial, the research team will ascertain which aspect(s) of the trial the participant wishes to withdraw from.

The aspects of the trial that the participant may request to withdraw from are as follows:

- No longer willing to complete study questionnaires
- No longer willing to provide research blood samples
- No longer willing to provide stool samples
- No longer willing to have study MRIs
- No longer willing to attend study visits
- No longer willing to be contacted by the site research team to obtain CRF/outcome data
- No longer willing to have standard of care data from the medical record provided to the study (e.g. standard care blood results)
- No longer willing to allow samples and linked clinical data to be used in future research
- No longer willing for contact details to be retained in order to provide summary of findings at the end of the study

Where a participant wishes to withdraw from all aspects of trial participation detailed above this will be considered a full trial withdrawal.

In addition to participant self-withdrawal, the PI (or delegate) may decide to withdraw a participant from the trial for clinical reasons or other reasons such as non-compliance, eligibility. Participants will still be asked to participate in the collection of follow-up data. The reason for withdrawal will be recorded on the trial Withdrawal CRF.

Completion of the Withdrawal CRF by the site research team will trigger a notification to the central CTU trial team. Appropriate action will be taken by the trial teams (centrally at the CTU and by the site research team at each participating site) to ensure compliance with the participant's withdrawal request. This may include marking future CRFs as not applicable and ensuring any relevant communications which the participant had consented to receive regarding their participation are no longer sent.

Data and samples collected up to the point of withdrawal will be used/analysed as explained in the PIS.

18 TRANSLATIONAL/ MECHANISTIC RESEARCH

Blood samples will be collected at screening and 24- week visit. Blood samples will be processed by sites after collection including spinning serum and isolating PBMCs from fresh blood. Processed samples will then be frozen for storage until completion of the trial for analysis to allow for batch processing.

The distribution of major immune cell populations will be accurately measured using flow-cytometry based on established cell markers and these immune cell subsets will be correlated with the extent of liver disease and clinical response to therapy.

Additional immunophenotyping will be performed using CyTOF (Cytometry by Time-Of-Flight); transcriptional profiling by single cell sequencing and cell-subset specific gene expression analysis of CD4+, CD8+, CD56+ and CD14+ cells and other key cell types will be undertaken. Plasma and serum will be analysed for protein and other analytes including genetic markers.

Plasma and serum will also be stored for measurement of additional cytokines including circulating MAIT-cell activation cytokines (IL-12 and IL-18 [29]), to help understand the signals driving MAIT-cell function.

Stool samples will be collected for microbiome analysis shortly after the screening visit and again shortly following the 24- week visit, and participants will return these by post. Stool will be fixed in ethanol and bacterial DNA extraction will be performed in batches at the end of the trial following previously published protocols[30]. Participants will complete a diet questionnaire for the 7-days preceding the stool sample collection, which will include any recent antibiotic use. The 16S ribosomal RNA (rRNA) gene will be sequenced to assess microbial composition, and both relative species abundance and diversity indices will be estimated. Microbiome profiles will be correlated with the immune signatures identified from blood-based immunophenotyping and molecular profiling.

19 QUALITATIVE RESEARCH

No qualitative research will be performed as part of the trial.

20 BLINDING AND CODE BREAKING

20.1 Blinding

There is no blinding in this trial.

21 TRIAL SAMPLES

21.1 Collection/use of new trial samples

Table 6 provides a summary of all samples required by this trial protocol.

Table 6: Summary of sampling requirements

Sample	Time point(s)	Optional consent sample?	Purpose (types of test or analysis)	Analysis by local NHS Trust lab or other laboratory	Results reported to site research team
5 mL blood (Standard of care)	Screening and 24-week visit	No	CRP	Local NHS laboratory as per usual site arrangements.	*N/A – data entered by site into REDCap*
5 mL blood (Standard of care)	Screening and 24-week visit	No	FBC	Local NHS laboratory as per usual site arrangements	*N/A- data entered by site into REDCap*
5 mL blood (Standard of care)	Screening and 24-week visit	No	LFT	Local NHS laboratory as per usual site arrangements.	*N/A – data entered by site into REDCap*
5 mL blood (Research sample)	Screening and 24-week visit	No	ELF	Local NHS laboratory if available or 3rd party laboratory	Yes – data entered into REDCap by site or central CTU team

Sample	Time point(s)	Optional consent sample?	Purpose (types of test or analysis)	Analysis by local NHS Trust lab or other laboratory	Results reported to site research team
40 mL blood (Research sample)	Screening and 24-week visit	No	PBMC and plasma for mechanistic evaluation of impact of Bimekizumab on inflammation	Central laboratory at University of Oxford	No
5 mL blood (Research sample)	Screening and 24-week visit	No	Serum for Mechanistic evaluation of impact of Bimekizumab on inflammation	Central laboratory at University of Oxford	No
Stool samples (Research sample)	Screening and 24-week visit	No	Determine gut flora composition, correlation with the disease process and impact of Bimekizumab on inflammation	Central laboratory at University of Oxford	No

21.2 Use of residual or existing samples

No existing samples will be utilised in this trial. Any residual samples at the end of this study may be transferred to a biobank with patient consent for future ethically approved research.

21.3 Sample handling for samples to be analysed in local NHS Trust laboratories

Samples to be analysed in local NHS Trust laboratories will be taken and processed by laboratories in accordance with local site practice. This includes labelling of samples with standard patient identifiers. Results will be reported back in the usual way according to local practice and accessed by the site research team. Such samples will be stored, held, reported and subsequently destroyed in accordance with standard local laboratory practice. If the local NHS Trust laboratory does not perform ELF blood test, a third-party laboratory, contracted by the Sponsor, will carry out the ELF testing.

21.4 Sample handling for samples analysed in a third-party or central laboratory

Sample handling (including any local processing) and storage will be managed according to separate written instructions/sample handling manual. Table 7 summarises the central and third-party laboratories used for the trial.

Table 7: Samples analysed by central laboratories.

Sample	Laboratory	Tests to be undertaken
Blood • Plasma • PBMCs • Serum	Central laboratory at University of Oxford	Flow-activated cell sorting (FACS) Immunophenotyping using CyTOF Single-cell RNA sequencing Cell subset specific gene expression analysis of CD4+, CD8+, CD56+ and CD14+ cells and other key cell types Analysis for protein and other biomarkers including genetic markers. Measurement of other key cytokines including circulating MAIT activation cytokines
Blood	Third-party laboratory (contracted by Sponsor)	ELF (for research sites where ELF testing not available within NHS laboratory)
Stool	Central laboratory at University of Oxford	Microbiome analysis

21.4.1 Provision of sample collection packs

A pack for collection of the screening and 24-week stool samples will be provided at those trial visits. Participants can then post these back to the central laboratory in a pre-paid pack. The site teams will follow up with participants to remind them if samples are not received.

21.5 Labelling and confidentiality of trial-specific samples

All samples sent to central laboratories will be labelled with the trial name, participant ID (their unique trial number), participant initials, and date taken. Should a central laboratory receive any samples carrying direct personal identifiers the recipient must immediately obliterate this information and re-label and report a data breach immediately to the central CTU trial team in addition to following any local reporting requirements.

21.6 Clinical reporting of (e.g. exploratory objectives/samples analysed by a central lab)

The results of the laboratory central assays are not intended to influence the individual participant's medical care. The findings will not be reported to trial participants or the site research teams.

21.7 Retention of samples at the end of the trial

The CI has overall responsibility for custodianship of the trial samples. Laboratories are instructed to retain any surplus samples pending instruction from the CI on use, storage or destruction. Participants

in this trial will be invited to permit the collection and long-term retention of samples post-trial for use in possible other future research (which may or may not be linked to trial data). Consent for such retention of samples is optional and not a requirement of participation in the main trial. Participants who decline optional consent to this or fully withdraw from all aspects of the trial will have their sample(s) destroyed at the end of the trial.

Where consent has been given, at the end of the trial any surplus samples may be retained for use in other projects that have received ethical approval and appropriate consent is in place. Hence, any surplus trial samples may be transferred to an appropriate licensed facility.

22 IMAGING

Perspectum Ltd have developed an advanced cloud-based software suite called CoverScan™ which uses MRI scan data to quantify multiple organ health that characterises tissue steatosis, fibro inflammation and function in the liver, heart, lungs, kidneys, pancreas and spleen. This suite has enabled comprehensive characterisation of patients with multi-system conditions that affect the liver, such as diabetes and long COVID [31,32]. CoverScan™, is a UK Conformity Assessed (UKCA) and FDA 510(k)-cleared technology that will be used within its licensed intent for the BALANCE study. The study does not evaluate, validate, or investigate the safety or performance of the software; it is used solely as a tool to analyse MRI images acquired as part of the study.

All participants will receive an MRI scan pre-treatment and 24 weeks post-treatment. All MRI scans will be acquired locally by trained site imaging staff within the NHS Trust or Perspectum's MRI facility using standard MRI equipment and an MRI acquisition protocol specified by Perspectum. No physical devices will be supplied or installed at site. The MRI acquisition protocol will be provided to sites in a study specific scanning manual and imaging staff at sites will receive study specific training from Perspectum prior to site activation.

De-identified MRI Digital Imaging and Communications in Medicine (DICOM) images will be uploaded by site imaging staff to the secure the Perspectum portal for analysis using its CoverScan™ software so that measurements of cT1 level and PDFF can be used to assess liver inflammation and fibrosis before and after initiation of treatment. By conducting the CoverScan™ this will also allow exploration of tissue steatosis, fibroinflammation and function in other organs in addition to the liver.

The CoverScan™ software introduces no additional risks beyond those associated with standard MRI scanning. All MRI procedures will be conducted in accordance with local clinical practice and established MRI safety procedures. No additional safety precautions are required beyond standard MRI operating procedures.

23 SAFETY REPORTING

23.1 Safety reporting period

Safety reporting for each participant will begin from time of consent and will end when the participant has reached their final follow-up time point at 24-weeks.

23.2 Definitions

An adverse event (AE)	Any untoward occurrence in a clinical trial participant.

	Note: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporarily associated with the trial procedures, whether or not considered related to the procedures.
Related Adverse Event	An event that resulted from administration of any of the research procedures
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening[1] • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • is a congenital anomaly/birth defect • is otherwise considered a medically important event by the Investigator[2]
Unexpected Related Serious Adverse Event	A serious adverse event related to the trial (i.e. resulted from administration of any of the research procedures) and is unexpected (not listed in the protocol as an expected occurrence).

[1] 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.

[2] Other 'important medical events' are any events that may jeopardise the participant or may require medical or surgical intervention to prevent one of the above outcomes listed above.

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

23.3 Expected adverse events

Bimekizumab is a licensed treatment and is being provided as part of the participant's routine NHS care. Expected AEs of Bimekizumab are detailed in the published summary of product characteristics (SmPC).

There are no expected AEs from the trial procedures (MRI scans/blood draw).

23.4 Recording and reporting of AEs/SAEs

23.4.1 Safety events deemed unrelated to Bimekizumab or trial procedures

AEs and SAEs that occur and are deemed unrelated to Bimekizumab or trial procedures (MRI scans/blood draw) do not require reporting except for the death of a participant which should be reported on the Death CRF within REDCap.

23.4.2 Safety events deemed related to Bimekizumab

AEs that occur and are deemed related (possibly, probably, or definitely) to Bimekizumab should be reported to the central CTU trial team on an AE form as soon trial team become aware of the AE and should be followed up either until resolution, the event is considered stable or the participant completes their final trial visit at which point they will be followed-up within standard care.

SAEs that occur and are deemed related (possibly, probably, or definitely) to Bimekizumab should be reported to the central CTU trial team on an SAE form immediately and under no circumstances should this exceed 24 hours following knowledge of the event being defined as serious.

Potential Hy's Law cases should be reported to the central CTU trial team on an SAE form within 24 hours of becoming aware of the event even before other possible causes of liver injury have been excluded. Potential Hy's Law Case Criteria:

- ≥ 3 Upper Limit of Normal (ULN) of ALT or AST and
- Total Bilirubin ≥ 2 ULN and
- Excluding patients ≥ 2 ULN alkaline phosphatase

23.4.3 Safety events deemed related to trial procedures

AEs that occur and are deemed related to trial procedures (MRI scans/blood draw) do not require reporting to the central CTU trial team.

SAEs that occur and are deemed related (possibly, probably, or definitely) to any of the research procedures (MRI scans or blood draw) will be considered unexpected and therefore require reporting to the central CTU trial team on an SAE form within 24 hours.

23.5 Events exempt from immediate reporting as a SAE

Only the SAEs, including the Potential Hy's Law cases, described in section 23.4.2 and 23.4.3 require expedited reporting.

23.6 Procedure for collecting safety events from sites/participants

Participants will be asked about any AEs at the week 24 follow-up visit.

23.7 Reporting of SAEs from sites to the CTU trial team

Only reportable SAEs as detailed in Section 23.4 will be reported immediately to the central CTU trial team. Such events will be reported immediately to the central CTU trial team as follows:

SAEs will be reported by the site research team using the SAE form within REDCap within 24 hours of becoming aware of the event. REDCap will auto-generate a unique SAE number when the SAE is first saved. The central CTU trial team is automatically notified of the SAE report via REDCap. A paper SAE form must be used as a back-up if the SAE form is not available electronically. This should be emailed to balance@ndorms.ox.ac.uk **within 24 hours of becoming aware of the event.** The central CTU trial team will acknowledge receipt of any SAEs reported via email within one working day.

23.8 Follow-up of SAEs

A follow-up report must be completed when the SAE resolves, is unlikely to change, or when additional information becomes available. If the SAE is an unexpected, related event then additional follow-up information must be provided as requested by the central CTU trial team.

23.9 Assessment of SAEs by the PI (or delegate)

The PI (or delegated individual) is responsible for assessing all reported SAEs for seriousness, causality and expectedness. Expectedness for events related to Bimekizumab will be determined according to the information listed in the SmPC for Bimekizumab (Section 4.8) available at the time of the event.

23.9.1 Relatedness/causality

The assessment of "relatedness" to the trial intervention is the responsibility of the PI at site or an agreed designee according to the following definitions:

Relationship to intervention	Attribution (Causality)	Description

Unrelated	Unrelated	The AE is clearly NOT related to the intervention
	Unlikely	The AE is doubtfully related to the intervention
Related	Possible	The AE may be related to the intervention
	Probable	The AE is likely related to the intervention
	Definite	The AE is clearly related to the intervention

For the purpose of safety reporting the intervention is defined as treatment with Bimekizumab or any specific trial intervention (e.g. MRI scan, clinical assessment, sample collection).

23.10 Review of SAEs by the Sponsor/CTU Nominated Person

An appropriately qualified person will review the SAE and raise any queries with the reporting site. If the site has not provided an assessment of causality and has not responded to the query, it will be assumed that the event reported is related to the trial procedures/intervention. The reporting site will be encouraged to respond and if a response is not provided the CI will be consulted by the CTU and the CTU will complete the Sponsor part of the SAE report.

23.11 Reporting of SAEs to the Research Ethics Committee (REC)

All SAEs that are assessed as related and unexpected will be submitted to the REC within 15 days of the CTU/Sponsor becoming aware of the event.

23.12 Unblinding of SAEs for reporting to the REC

Not applicable. There is no blinding in this trial.

23.13 Reporting of safety events to Funder

All reports of AE/SAEs deemed related to Bimekizumab will be shared by the central CTU trial team with the Funder UCB – this will only contain de-identified data.

24 PREGNANCY

Pregnancies occurring while participating in this trial will be managed as per standard care for this population.

Participants who become pregnant may continue in the trial but further MRI scans should not be performed. A withdrawal form, withdrawing the participant from further MRI scans should be completed. Decisions on continuation/discontinuation of the drug Bimekizumab will be made by the treating clinical team.

In the event a participant becomes pregnant, no additional pregnancy information (including notification details, clinical data, or outcomes) will be collected for the purposes of the trial.

25 STATISTICAL CONSIDERATIONS

25.1 Statistical Analysis Plan (SAP)

No separate statistical analysis plan will be produced for this trial. The statistical aspects of the trial for the primary and secondary objectives are summarised here.

25.2 Sample Size

There is no formal sample size calculation due to limited data available from previous studies. With multi-organ imaging to investigate prevalence of fibro inflammation in other organs and impact of treatment we assumed a minimum sample size of 25 participants based on an effect seen within the COLIPSO trial (unpublished result) in LiverMultiscan™ with IL-17A inhibitors treatment and being above the scan-rescan repeatability for pancreas srT1. To allow for a small dropout rate, we plan to include 30 participants (aiming for 15 PsO participants and 15 PsA participants). Recruitment for one condition will not be stopped once 15 are reached, recruitment will be stopped once 30 overall have been registered, pre-treatment MRI scans completed and Bimekizumab started.

25.3 Description of Statistical Methods

Results will be reported in line with the STROBE statement and any appropriate extensions.[33] A single final statistical analysis will take place after all follow-up has been completed, and sufficient time has been allowed for data collection and cleaning.

Baseline characteristics will be summarised descriptively by PsO and PsA participants and overall. Summaries will be numbers and proportions for binary and categorical variables and means and standard deviations, medians and interquartile ranges for continuous variables.

AEs will be summarised by the number of participants experiencing each type of event. The grades and causality will be reported.

It is anticipated that all statistical analysis will be undertaken using Stata (StataCorp LP, www.stata.com), R (https://www.r-project.org/) or other validated statistical software.

25.3.1 Primary outcome

CoverScan™ liver measurements (median liver cT1 and median liver PDFF) will be summarised pre-treatment and 24 weeks post-treatment via boxplots or other appropriate graphical displays. A paired t-test or a non-parametric alternative (if assumptions for the t-test do not hold) will be also carried out and 95% confidence intervals will be reported.

The percentage of participants with liver cT1 level >=800ms and mean PDFF>5.5% will be summarised at pre-treatment and 24 weeks post-treatment with numbers and proportions. A test of equality of proportions between the two time points will be carried out for both measures if appropriate.

25.3.2 Secondary outcome(s)

CoverScan™ measurements of other organs (MRI biomarkers of fibro-inflammation in heart, lungs. kidneys, pancreas and spleen)[32] will be summarised descriptively at the two time points and via boxplots (continuous measurements) and bar plots for (categorical or binary measurements) or other appropriate graphical displays.

Clinical measures of disease activity and, patient- reported outcome measures will be summarised descriptively at pre-treatment and 24 weeks post-treatment.

Associations between CoverScan™ measurements and PASI and Disease Activity Index for Psoriatic Arthritis (DAPSA) scores will also be reported.

25.4 Subgroup analyses

Clinical measures of disease activity and patient-reported outcome measures at 24 weeks will be summarised descriptively by PsO and PsA participant groups overall.

Mean or median differences of CoverScan™ liver measurements between PsO and PsA participants will be estimated at 24 weeks, and 95% confidence intervals will be reported. Adjusted mean differences will also be reported by fitting linear regression models adjusting for appropriate covariates (alcohol consumption, BMI etc) and pre-treatment scores.

No formal comparison will be made between PsO and PsA results and any subgroup analyses reported will be labelled as exploratory.

25.5 Interim analyses

There is no planned interim analysis.

25.5.1 Stopping rules

An independent TOC will review the accumulating data at regular intervals and may recommend pausing or stopping the trial in the event of safety concerns.

25.6 Level of Statistical Significance

If statistical tests are performed, a significance level of 5% will be used and results will be reported with 95% confidence intervals.

25.7 Procedure for accounting for missing data

The trial will attempt to collect data as completely as possible. The total sample size has incorporated an inflation to account for potential loss to follow-up or participant death.

Missing data for the primary outcome are expected to be minimal, therefore any missing data will be described and not otherwise accounted for in the analysis. Missing data for patient-reported outcomes will be investigated and sensitivity analyses will be performed to assess the impact of missing data and the robustness of findings.

The procedure for handling spurious or missing data will be detailed in the Data Management Plan. The trial will attempt to collect data as completely as possible.

25.8 Procedures for reporting any deviation(s) from the original statistical analysis plan

Any deviation(s) from this plan will be described in the final statistical report.

25.9 Internal pilot/Decision Points

No internal pilot is planned.

25.10 Inclusion in analysis

All patients eligible for the trial and who consented and received at least one dose of Bimekizumab will be accounted for and included in the analyses. The number of participants who were not evaluable, who died or withdrew before starting Bimekizumab will be recorded. The number of participants lost to follow-up will also be reported.

26 HEALTH ECONOMICS

There are no health economic analyses to be undertaken as part of the trial.

27 DATA MANAGEMENT

The data management aspects of the trial are summarised here with details fully described in the trial-specific Data Management Plan.

27.1 Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no prior written or electronic record of data). The MRI source data consist of the raw DICOM files and associated acquisition metadata generated at the imaging site. Source data for the trial is detailed in the tables within section 9 and defined further within the trial Data Management Plan.

27.2 Case report forms (CRFs)

The PI and trial site staff will ensure that data collected on each participant is recorded in the CRF as accurately and completely as possible within 5 working days of each visit. Details of all protocol evaluations and investigations must be recorded in the participant's medical record. All appropriate laboratory data, summary reports and Investigator observations will be transcribed into the CRFs from the relevant source data held in the site medical record(s).

All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent and GP letter, the participant will be referred to by the trial participant number/code, not by name.

27.3 Non-CRF data

The data generated that will not be recorded on a trial CRF/ entered into REDCap are listed in Table 8. Further detail about the management and use of non-CRF data is within the trial Data Management Plan.

Table 8: Non-CRF data

Non-CRF data
Data generated by Perspectum from MRI scans
Data generated from central laboratory from blood samples
Data generated from central laboratory from stool samples
Data from participant completed diet questionnaires[1]
Protocol deviations which do not relate to a specific participant

[1] Information collected through the diet questionnaire will not be incorporated into the statistical analyses of the trial. Instead, these data will be used to support and inform the interpretation of the microbiome results.

27.4 Access to Data

Members of the local research team and central CTU trial team will only be able to access data that they need to, based on their roles and responsibilities within the trial.

Direct access to source data/documents will be required for trial-related monitoring and/or audit by the Sponsor, central CTU trial team or NHS Trust or regulatory authorities as required.

The data submitted by trial participants directly in REDCap (i.e. electronic patient- reported outcomes) will also be made available to the participating site that recruited the participant; this is detailed within the PIS so that participants are aware of who will have access to this data.

27.5 Data Recording and Record Keeping

The CRFs will be designed by members of the central CTU trial team which will include the CI, trial statistician(s) and trial manager.

Data will, wherever possible, be collected in electronic format with direct entry into REDCap by site staff or participants. Electronic data collection has the major advantage of building "data logic" into forms, minimising missing data, data input errors and ensuring the completeness of consent and assent forms. REDCap is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

All data entered will be encrypted in transit between the client and server. All electronic patient-identifiable information, including electronic consent forms, will be held on a server located in an access-controlled server room at the University of Oxford.

The data collection system and server are backed up to a secure location on a regular basis. Details of the data collected, where it is stored and who has access to it along with a fair processing statement will be available for the participants within the trial PIS.

27.6 Electronic transfer of data

Any electronic transfer of data within the University of Oxford or from the University of Oxford to external parties during the course of the trial will be strictly controlled in accordance with the Oxford Clinical Trial Research Unit's (OCTRU) SOP for Secure Information/Data Transfer. All the metrics from the MRI scans will be transferred securely from Perspectum. The lab data for further analysis will also be transferred following the rules above.

28 QUALITY ASSURANCE PROCEDURES

A rigorous programme of quality control will be implemented. The Trial Management Group (TMG) will be responsible for ensuring adherence to the trial protocol at the trial sites. Quality assurance (QA) checks will be undertaken by OCTRU to ensure trial entry procedures and data collection. OCTRU has a QA team who will monitor this trial and conduct audits in accordance with their SOPs. Furthermore, the processes of receiving consent, registration, provision of information will be monitored by the central CTU trial team. Additionally, the trial may be monitored or audited by Sponsor or host sites in accordance with the current approved protocol, GCP, relevant regulations and SOPs.

A trial-specific data management and monitoring plan will be in place prior to the start of the trial.

28.1 Risk Assessment

This protocol is designed to deliver a risk-adapted approach to conducting the research. A risk assessment has been conducted and a monitoring plan will be prepared before the trial opens. The known and potential risks and benefits to participants have been assessed in comparison to those of standard of care. A risk management strategy is in place and will be reviewed and updated as

necessary throughout the trial or in response to outcomes from monitoring activities. Monitoring plans will be amended as appropriate.

28.2 Trial monitoring

Monitoring will be performed by the central CTU trial team according to a trial-specific monitoring plan. Data will be evaluated for compliance with the protocol, completeness and accuracy. The investigator and institutions involved in the trial will permit trial-related monitoring and provide direct on-site access to all trial records and facilities if required. They will provide adequate time and space for the completion of monitoring activities.

Trial sites will be monitored centrally by checking incoming data for compliance with the protocol, consistency, completeness and timing. The CRF data will be validated using appropriate set criteria, range and verification checks. The trial site must resolve all data queries in a timely manner (within no more than 10 working days of the data query unless otherwise specified). All queries relating to key outcome and safety data and any requiring further clarification will be referred back to the trial site for resolution.

Trial sites will also be monitored remotely and/or by site visit, as necessary, to ensure their proper conduct of the trial. Central CTU trial team staff will be in regular contact with site personnel to check on progress and deal with any queries that they may have. Any monitoring reports/data discrepancies will be sent to the site in accordance with OCTRU SOPs and the trial monitoring plan. The Investigator is expected to action any points highlighted through monitoring and must ensure that corrective and preventative measures are put into place as necessary to achieve satisfactory compliance, within 28 days as a maximum, or sooner if the monitoring report requests.

28.3 Audit and regulatory inspection

All aspects of the trial conduct may be subject to internal or external QA audit to ensure compliance with the protocol, GCP requirements and other applicable regulation or standards. Such audits may occur at any time during or after the completion of the trial. Investigators and their host Institution(s) should understand that it is necessary to allow auditors direct access to all relevant documents, trial facilities and to allocate their time and the time of their staff to facilitate the audit visit. Anyone receiving notification of an audit that will (or is likely to) involve this trial must inform the central CTU trial team without delay.

28.4 Trial committees

28.4.1 Trial Management Group (TMG)

A TMG will be established for the trial and operate in accordance with a trial-specific TMG charter. The TMG will manage the trial, including the clinical and practical aspects and will meet approximately monthly to assess progress. Other specialities/individuals will be invited as required for specific items/issues.

28.4.2 Data and Safety Monitoring Committee (DSMC)

There will be no DSMC for the trial because the trial does not have efficacy or safety endpoints. The TOC will cover both roles.

28.4.3 Trial Oversight Committee (TOC)

The TOC, which includes independent members, provides overall supervision of the trial on behalf of the funder. The TOC will act in accordance with a TOC charter which will outline its roles and

responsibilities. Full details including names will be included in the TOC charter. Meetings of the TOC will take place at least once a year during the recruitment period. An outline of the remit of the TOC is to:

- monitor and supervise the progress of the trial towards its interim and overall objectives
- review at regular intervals relevant information from other sources
- inform the funding body on the progress of the trial

29 IDENTIFICATION AND MANAGEMENT OF PARTICIPATING SITES

29.1 Identification of recruitment sites

Recruitment sites will be selected based on suitability to conduct the trial. Potential sites will be invited to complete a site feasibility questionnaire (SFQ) which will be used by the Trial Management Group to assess suitability of the site for the trial; the suitability assessment will primarily be based on the resources available at site and the feasibility of meeting recruitment targets.

29.2 Trial site responsibilities

The PI (or lead clinician for the trial site) has overall responsibility for the conduct of the trial but may delegate responsibility where appropriate to suitably experienced and trained members of the site research team. All members of the site research team must complete the delegation log provided by the central CTU trial team prior to undertaking any trial duties. The PI must counter sign and date each entry in a timely manner, authorising staff to take on the delegated responsibilities.

29.3 Trial site set up and activation

The PI leading the participating trial site is responsible for providing all required core documentation. Mandatory site training which is organised by the central CTU trial team (see below) must be completed before the site can be activated. Training in the trial processes will be administered at site initiation visits delivered either in person or online by the central CTU trial team. The central CTU trial team will check to confirm that the site has all the required trial information/documentation and is ready to recruit. The site will then be notified once they are activated on the REDCap data collection system and are able to begin recruiting participants.

29.4 Training

Training in the trial processes will be administered at site initiation visits (delivered face to face or online) by the central CTU trial team.

29.5 Trial documentation

The central CTU trial team will provide an electronic ISF to each participating site containing the documents needed to conduct the trial. The central CTU trial team must review and approve any local changes made to any trial documentation including patient information and consent forms prior to use. Additional documentation generated during the course of the trial, including relevant communications must be retained in the site files as necessary to reconstruct the conduct of the trial.

30 ETHICAL AND REGULATORY CONSIDERATIONS

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki, the principles of GCP, the UK Data Protection Regulation (UK GDPR) and all other applicable regulatory and governance frameworks including the UK policy framework for health and social care research.

30.1 Summary of trial-specific considerations

In the unlikely event of seeing any structural abnormalities on a scan, the scan will be checked by a clinical specialist. If the specialist feels that the abnormality is medically important, these findings will be discussed with the PI at the local research site and further investigations arranged as necessary. Participants will not be informed unless the PI considers the finding has clear implications for their current or future health. It is important to note that scans are not carried out for diagnostic purposes, and therefore the scans are not a substitute for a clinical appointment. Rather, the scans are intended for research purposes only.

30.2 Ethical conduct of the trial and ethical approvals

The protocol, PIS, ICF and any other information that will be presented to potential trial participants (e.g. advertisements or information that supports or supplements the informed consent process) will be reviewed and approved by an appropriately constituted, independent REC.

30.3 NHS Research Governance

Once Health Research Authority (HRA) & Health and Care Research Wales (HCRW) approval is in place for the trial, sites will confirm capability and capacity to participate in the trial.

30.4 Protocol amendments

All amendments will be generated and managed according to OCTRU SOPs to ensure compliance with applicable regulation and other requirements. Written confirmation of all applicable REC and local approvals must be in place prior to implementation by Investigators as applicable for the amendment type. The only exceptions are for changes necessary to eliminate an immediate hazard to trial participants (see below).

It is the PI's responsibility to update participants (or their authorised representatives, if applicable) whenever new information becomes available that might affect the participant's willingness to continue in the trial. The Investigator must ensure this is documented in the participant's medical notes and the participant is re-consented if appropriate.

30.5 Protocol Compliance and Deviations

Protocol compliance is fundamental to GCP. Prospective, planned deviations or waivers to the protocol are not allowed. Changes to the approved protocol need prior approval unless for urgent safety reasons.

A trial related deviation is a departure from the ethically approved trial protocol or other trial document or process or from GCP or any applicable regulatory requirements. Deviations from the protocol will be captured in REDCap using either using a protocol deviation form or via suitably designed fields within the CRF which will be extracted from REDCap and reviewed regularly by the TMG. Deviations will be handled and reviewed in a timely manner in accordance with a trial-specific Data Management and Monitoring Plan.

The PI must promptly report any important deviation from GCP or protocol to the central CTU trial team. Examples of important deviations are those that might impact patient safety, primary/ secondary endpoint data integrity, or be a possible serious breach of GCP (see section 30.8).

Any third parties conducting trial-specific procedures must also report any deviations directly to the central CTU trial team.

30.6 Urgent safety measures

The Sponsor or PI (or delegate) may take appropriate urgent safety measures to protect trial participants from any immediate hazard to their health or safety. Urgent safety measures may be taken without prior authorisation. The trial may continue with the urgent safety measures in place. **The Investigator must inform the central CTU trial team IMMEDIATELY if the trial site initiates an urgent safety measure:**

The notification must include:

- Date of the urgent safety measure;
- Who took the decision; and
- What action was taken and why

The PI (or delegate) will provide any other information that may be required to enable the central CTU trial team to report and manage the urgent safety measure in accordance with the current regulatory and ethical requirements for expedited reporting and close out. The central CTU trial team will follow written procedures to implement the changes accordingly.

30.7 Temporary halt

The Sponsor and Investigators reserve the right to place recruitment to this protocol on hold for short periods **or** to declare a temporary halt. A temporary halt is defined as a formal decision to:

- stop recruitment on safety grounds; or
- stop recruitment for any other reason(s) considered to meet the substantial amendment criteria, including possible impact on the feasibility of completing the trial in a timely manner.

The central CTU trial team will report the temporary halt to the REC via an expedited substantial amendment procedure. The trial may not restart after a temporary halt until a further substantial amendment to re-open is in place. If it is decided not to restart the trial this will be reported as an early termination.

30.8 Serious Breaches

A “serious breach” is a breach of the protocol or of the conditions or principles of GCP 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.

Investigators must notify the central CTU trial team within one working day if any serious breach of GCP is suspected. The central CTU trial team will review the event and, if appropriate will report a serious breach to the REC and the NHS host organisation within 7 days of the central CTU trial team becoming aware of the breach.

30.9 Trial Reports

This protocol will comply with all current applicable REC and Sponsor reporting requirements.

30.10 Transparency in Research

Prior to the recruitment of the first participant, the trial will be registered on a publicly accessible database (ISRCTN), which will be kept up to date during the trial, and results will be uploaded to the registry within 12 months of the end of the trial declaration. A Final Report will be submitted to the REC containing a lay summary of the trial results which will be published on the HRA website.

The results of the trial will be published and disseminated in accordance with the section 0.

30.11 Use of social media

Social media (e.g. Twitter feeds) may be utilised by the central CTU trial team to make general announcements about the trial and acknowledge when milestones are met (e.g. sites open to recruitment, first recruitment ay a site etc).

31 PARTICIPANT CONFIDENTIALITY

31.1 Collection and use of personal identifiable data (PID)

PID will be collected and used in this trial as detailed in Table 9.

Table 9: Collection and use of personal identifiable data

Personal identifiable information collected	Planned use in trial
Participant full name	Collected during the consent process To send the summary of findings from the trial (at the end of the trial) To organise the MRI scan appointment for participants from one research site
Participant signature (handwritten/ e-signature)	Collected during the consent process
Participant date of birth	To organise the MRI scan appointment for participants from one research site
Participant postal address	To send the summary of findings from the trial (for any participants that consent and wish to receive a copy by post)
Participant E-mail address	To send copy of consent form (for any participants that consent electronically and wish to receive a copy by email) To organise the MRI scan appointment for participants from one research site To send questionnaires (for any participants who wish to complete remotely at home) To send the summary of findings from the trial (for any participants that consent and wish to receive a copy by email)
Participant telephone number	To organise the MRI scan appointment for participants from one research site
Participant sex	To describe the study population To include as a variable in the analysis of the MRI data

The PIS explains what PID will be collected and how these will be used.

Site staff at participating sites will ensure that contact details for trial participants are up to date when participants attend for trial visits or are contacted about the trial.

31.2 Use of audio /visual recording devices

No audio/ visual recording devices will be used.

31.3 Storage and use of personal data

During the trial, personal data will be stored and used in accordance with the Oxford Clinical Trial Research Unit's (OCTRU) SOP for confidentiality, protection and breach of personal data in relation to research participants. This ensures that all personal data collected during the trial is recorded, handled and stored in accordance with the requirements of the UK General Data Protection Regulation (UK GDPR).

All electronic participant-identifiable information will be held on a secure, password-protected database accessible only to authorised personnel. If used, paper forms with patient-identifiable information will be held in secure, locked filing cabinets within a restricted area. The processing of the personal data of participants will be minimised wherever possible by the use of a unique participant trial number on trial documents and any electronic systems.

Personal data on all documents will be regarded as confidential. The trial staff will safeguard the privacy of participant's personal data.

The use of all personal data in the trial will be documented in a trial-specific data management plan which details what and where personal data will be held, who will have access to the data, when personal data will be anonymised and how and when it will be deleted.

The Investigator site will maintain the patient's anonymity in all communications and reports related to the research.

Data Breaches will be highlighted to the relevant site staff and reported as required by the UK GDPR and Data Protection Act 2018. This will also be deemed a protocol deviation.

31.4 Access to participants' PID during the trial

Access to participants PID will be restricted to individuals authorised to have access. This includes a) members of the site research team at participating trial sites with delegated responsibility by the site PI and b) members of the central CTU trial team involved in the conduct/management of the trial where this is necessary for their role and c) Perspectum who may arrange MRI scans for participants.

Research staff that are not part of the potential participant's direct healthcare team will not have access to PID until the individual has given their consent to take part in the trial or the participant has indicated to their direct healthcare team that they wish to be contacted by a member of the site research team – permission for this will be recorded in the individual's medical notes.

The PIS clearly describes who will have access to the participants PID during the trial.

Participants will be asked to consent to relevant sections of their medical notes and data collected during the trial being looked at by individuals from the University of Oxford, from regulatory authorities [and from the NHS Trust(s)], where it is relevant to their taking part in this trial; only authorised individuals will be granted access where this is necessary for their role.

31.5 Destruction of PID

PID will be destroyed as soon as it is no longer required – the time point for this destruction is detailed in the trial data management plan and is in accordance with OCTRU SOPs which comply with the UK GDPR.

31.6 Participant Identification Log

The site research team must keep a separate log of enrolled patients' personal identification details as necessary to enable them to be tracked. These documents must be retained securely, in strict confidence. They form part of the ISF and are not to be released externally.

32 PUBLIC AND PATIENT INVOLVEMENT (PPI)

32.1 PPI in trial design and protocol development

Studying liver disease in PsA, has been highlighted as a priority in the James Lind Alliance PSP for PsA and discussions with PsA patients in the team have highlighted the interest in liver disease.

Patient partners will be recruited to the TOC and will be involved during the protocol development.

32.2 PPI in development of participant information

Patient research partners will review the participant-facing information for the trial to ensure that this is well-written in lay language and clear for potential participants.

32.3 PPI during the trial

Patient partners will be recruited to the TOC and will be involved throughout the trial process.

33 EXPENSES/PAYMENTS TO PARTICIPANTS

Participants have the option to claim up to £30 for reimbursement for travel (using their own car, public transport or taxi) to attend hospital visits that are additional to usual care (Screening and Follow-up Clinic Visits and MRI scan appointments if arranged separately to the participant's usual care appointment). Travel expenses will be paid upon production of receipts or a mileage allowance provided as appropriate. Claims will be submitted to the trial site who will pay travel expenses to the participant. Trial sites will invoice the Sponsor for travel expenses paid to participants.

34 SPONSORSHIP, FINANCE, AND INSURANCE

34.1 Sponsorship

The Sponsor will provide written confirmation of Sponsorship.

34.2 Funding and support in kind

Table 10: Details of trial funding provides a summary of all funding and support in kind for the trial.

Table 10: Details of trial funding

Funder(s)	Financial and non-financial support given
UCB	Financial support for trial

34.3 Insurance

The University of Oxford 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.

35 CONTRACTUAL ARRANGEMENTS

This trial is subject to the Sponsor's policy requiring that written contracts/agreements are agreed formally by the participating bodies as appropriate.

Appropriate contractual arrangements will be put in place with all third parties.

36 PUBLICATION AND DISSEMINATION

The Sponsor will retain ownership of all data arising from the trial.

Publication and dissemination of trial results will be in accordance with OCTRU SOPs and irrespective of trial findings.

36.1 Trial results

All data will be presented such that no individual participants can be identified.

36.2 Informing participants of trial results

A summary of the trial results for trial participants will be written collaboratively with clinicians and patient representatives and distributed according to participant's preference when joining the trial.

36.3 Dissemination of trial results

Dissemination of results will include the following methods:

Conferences: The results of this trial will be disseminated to the clinical community via presentations at national and international meetings. Traditional conference dissemination will focus on presentations to include the key professional stakeholders. It is expected that findings from this trial will be presented at national and international conferences.

Publications: Results will usually be published in peer-reviewed journals. Where possible, plain English summaries will be published alongside the full paper.

Public Dissemination: The wider public will be alerted using lay summaries and via links with relevant charities and organisations.

36.4 Authorship

Authorship of any publications arising from the trial will be determined in accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines and any contributors acknowledged accordingly.

All publications arising from this trial must acknowledge the contribution of participants, funder(s), OCTRU, BALANCE and the Sponsor.

37 DEVELOPMENT OF A NEW PRODUCT/PROCESS OR THE GENERATION OF INTELLECTIAL PROPERTY (IP)

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

38 ARCHIVING

38.1 Archiving period

The minimum mandatory archiving period for essential trial documents for this trial is 15 years following publication. Participating sites must not archive or destroy study essential documents or samples without written instruction from the central CTU trial team.

38.1.1 Retention of documents/information beyond the mandatory archiving period

The following documents will be retained longer:

- ICFs for samples used beyond the life of the trial; these will be retained for the life of the sample to meet HTA traceability requirements.
    - These will be stored by the Oxford Musculoskeletal Biobank

38.2 Archiving responsibilities/procedure

During the trial and after trial closure the PI must maintain adequate and accurate records to enable the conduct of the clinical trial and the quality of the research data to be evaluated and verified. All essential documents must be stored in such a way that ensures that they are readily available, upon request for the minimum period as specified above.

38.2.1 CTU TMF

All paper and electronic data including the TMF and trial data collection system(s) will be retained and archived in accordance with OCTRU's SOPs which are compliant with the UK GDPR.

38.2.2 Investigator Site File and participant medical records

The ISFs will be archived at the participating site. The medical files of trial participants must be retained for the mandatory archiving period stated above and in accordance with the maximum period of time permitted by the participating site. Sites must comply with the documentation retention specified in the clinical trial agreements (or equivalent) issued by the trial Sponsor.

39 DATA SHARING

39.1 Data sharing during the trial

The data sharing arrangements during the trial are detailed in a separate Data Management Plan. Data will be shared only with the appropriate consent from the trial participant.

39.2 Data sharing at the end of the trial

The trial statistician (and CI) may retain copies of de-identified datasets for the purpose of data sharing in accordance with the trial data sharing plan.

Upon completion of the trial, de-identified research data may be shared with other organisations upon request. All requests for data sharing will be handled in accordance with the OCTRU SOP on Data Sharing and will be considered in accordance with the data sharing policies of OCTRU, the Sponsor and funder(s). De-identified data may also be used for teaching and learning purposes.

40 REFERENCES

1. Gisondi P, Targher G, Zoppini G, Girolomoni G. Non-alcoholic fatty liver disease in patients with chronic plaque psoriasis. *J Hepatol* 2009; **51**(4): 758-64.
2. Miele L, Vallone S, Cefalo C, et al. Prevalence, characteristics and severity of non-alcoholic fatty liver disease in patients with chronic plaque psoriasis. *J Hepatol* 2009; **51**(4): 778-86.
3. Madanagobalane S, Anandan S. The increased prevalence of non-alcoholic fatty liver disease in psoriatic patients: a study from South India. *Australas J Dermatol* 2012; **53**(3): 190-7.
4. Chiricozzi A, Romanelli P, Volpe E, Borsellino G, Romanelli M. Scanning the Immunopathogenesis of Psoriasis. *Int J Mol Sci* 2018; **19**(1).
5. Dey AK, Joshi AA, Chaturvedi A, et al. Association Between Skin and Aortic Vascular Inflammation in Patients With Psoriasis: A Case-Cohort Study Using Positron Emission Tomography/Computed Tomography. *JAMA Cardiol* 2017; **2**(9): 1013-8.
6. Mahmood F, Coates LC, Helliwell PS. Current concepts and unmet needs in psoriatic arthritis. *Clinical rheumatology* 2018; **37**(2): 297-305.
7. Persico M, Palmentieri B, Vecchione R, Torella R, de SI. Diagnosis of chronic liver disease: reproducibility and validation of liver biopsy. *Am J Gastroenterol* 2002; **97**(2): 491-2.
8. Banerjee R, Pavlides M, Tunnicliffe EM, et al. Multiparametric magnetic resonance for the non-invasive diagnosis of liver disease. *J Hepatol* 2014; **60**(1): 69-77.
9. Pavlides M, Banerjee R, Sellwood J, et al. Multiparametric magnetic resonance imaging predicts clinical outcomes in patients with chronic liver disease. *J Hepatol* 2016; **64**(2): 308-15.
10. Pavlides M, Banerjee R, Tunnicliffe EM, et al. Multiparametric magnetic resonance imaging for the assessment of non-alcoholic fatty liver disease severity. *Liver Int* 2017; **37**(7): 1065-73.
11. Harrison S, Wilman H, Kelly M, et al. Prevalence and stratification of NAFLD/NASH in a UK and US cohort using non-invasive multiparametric MRI. European Association for the Study of the Liver Annual Conference; 2018.
12. Eddowes PJ, McDonald N, Davies N, et al. Utility and cost evaluation of multiparametric magnetic resonance imaging for the assessment of non-alcoholic fatty liver disease. *Aliment Pharmacol Ther* 2018; **47**(5): 631-44.
13. McKay A, Wilman HR, Dennis A, et al. Measurement of liver iron by magnetic resonance imaging in the UK Biobank population. *PLoS One* 2018; **13**(12): e0209340.
14. Mojtahed A, Kelly CJ, Herlihy AH, et al. Reference range of liver corrected T1 values in a population at low risk for fatty liver disease-a UK Biobank sub-study, with an appendix of interesting cases. *Abdom Radiol (NY)* 2019; **44**(1): 72-84.
15. Arndtz K, Hodson J, Eddowes PJ, et al. Cross-sectional, prospective, evaluation of the utility of Multi-parametric MRI imaging in predicting clinically meaningful outcomes in autoimmune hepatitis. AASLD, The Liver Meeting. San Francisco; 2018.
16. James L, Diamond C, Al-Mossawi H, et al. High prevalence of MASLD in psoriasis and psoriatic arthritis assessed with multiparametric magnetic resonance imaging. *Rheumatology (Oxford)* 2025; **64**(11): 5741-50.
17. Scher JU, Ubeda C, Artacho A, et al. Decreased bacterial diversity characterizes the altered gut microbiota in patients with psoriatic arthritis, resembling dysbiosis in inflammatory bowel disease. *Arthritis Rheumatol* 2015; **67**(1): 128-39.
18. Kurioka A, Walker LJ, Klenerman P, Willberg CB. MAIT cells: new guardians of the liver. *Clin Transl Immunology* 2016; **5**(8): e98.
19. Walker LJ, Kang YH, Smith MO, et al. Human MAIT and CD8alphaalpha cells develop from a pool of type-17 precommitted CD8+ T cells. *Blood* 2012; **119**(2): 422-33.
20. Brough I, Thompson K, Latore C, et al. Elevated type-17 cytokines are present in axial spondyloarthritis stool. *Discov Immunol* 2024; **3**(1): kyae005.

21. McInnes IB, Mease PJ, Kirkham B, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2015; **386**(9999): 1137-46.
22. McInnes IB, Asahina A, Coates LC, et al. Bimekizumab in patients with psoriatic arthritis, naive to biologic treatment: a randomised, double-blind, placebo-controlled, phase 3 trial (BE OPTIMAL). *Lancet* 2023; **401**(10370): 25-37.
23. Merola JF, Landewe R, McInnes IB, et al. Bimekizumab in patients with active psoriatic arthritis and previous inadequate response or intolerance to tumour necrosis factor-alpha inhibitors: a randomised, double-blind, placebo-controlled, phase 3 trial (BE COMPLETE). *Lancet* 2023; **401**(10370): 38-48.
24. Teunissen MBM, Yeremenko NG, Baeten DLP, et al. The IL-17A-producing CD8+ T-cell population in psoriatic lesional skin comprises mucosa-associated invariant T cells and conventional T cells. *The Journal of investigative dermatology* 2014; **134**(12): 2898-907.
25. Menon B, Gullick NJ, Walter GJ, et al. Interleukin-17+CD8+ T cells are enriched in the joints of patients with psoriatic arthritis and correlate with disease activity and joint damage progression. *Arthritis Rheumatol* 2014; **66**(5): 1272-81.
26. Harrison S, Roberts K, Paredes AH, et al. Prospective prevalence study of adult NAFLD/NASH utilising multi-modality imaging compared with liver biopsy. European Association for the Study of the Liver Annual Conference; 2017.
27. Orbai AM, de Wit M, Mease P, et al. International patient and physician consensus on a psoriatic arthritis core outcome set for clinical trials. *Ann Rheum Dis* 2017; **76**(4): 673-80.
28. Day JW, Rosenberg WM. The enhanced liver fibrosis (ELF) test in diagnosis and management of liver fibrosis. *Br J Hosp Med (Lond)* 2018; **79**(12): 694-9.
29. Fergusson JR, Smith KE, Fleming VM, et al. CD161 defines a transcriptional and functional phenotype across distinct human T cell lineages. *Cell Rep* 2014; **9**(3): 1075-88.
30. Franzosa EA, Morgan XC, Segata N, et al. Relating the metatranscriptome and metagenome of the human gut. *Proc Natl Acad Sci U S A* 2014; **111**(22): E2329-38.
31. Dennis A, Wamil M, Alberts J, et al. Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. *BMJ Open* 2021; **11**(3): e048391.
32. Diamond C, Pansini M, Hamid A, et al. Quantitative Imaging Reveals Steatosis and Fibroinflammation in Multiple Organs in People With Type 2 Diabetes: A Real-World Study. *Diabetes* 2024; **73**(8): 1285-99.
33. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**(9596): 1453-7.

41 VERSION HISTORY

Previous versions of this protocol and a summary of the changes made are listed below.

Protocol version no.	Protocol date	Summary of key changes from previous version
N/A		1st version of the protocol – delete if using template for an amendment

APPENDIX 1 – TRIAL FLOW CHART