Decision on optimal combinatorial therapies in immune-mediated inflammatory diseases using systems approaches (DocTIS): protocol for a single-arm, adaptive basket trial in rheumatoid and psoriatic arthritis

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ABSTRACT

Background: Current treatments for rheumatoid arthritis (RA) and psoriatic arthritis (PsA) reduce disease activity but often fail to achieve sustained remission. The DocTIS programme has shown that additive anti-inflammatory effects in patients with arthritis can be achieved by combining tumour necrosis factor (TNF) and interleukin-6 (IL-6) inhibitor therapies.

Objectives: To provide proof-of-principle evaluation of whether combining TNF and IL-6 inhibitors shows a signal of activity on remission outcomes in RA and PsA.

Methods: This is a single arm, multi-centre, adaptive basket trial, recruiting 20 patients with RA and 20 with PsA, and including 24 weeks of treatment and 10 weeks of safety follow-up. Eligible participants on TNF for ≥6 weeks will proceed with the addition of IL-6 inhibitor (tocilizumab) at 162 mg every two weeks for 8 weeks, escalating to weekly dosing in weeks 9–24 if well tolerated. The primary outcome is remission at 24 weeks (Clinical Disease Activity Index (CDAI) score of ≤2.8 in RA, and Disease Activity in PsA (DAPSA) score of <4). Secondary outcomes include safety, tolerability, and disease activity assessments. Using Simon's two-stage design (80% power, one-sided $\alpha = 0.10$), the trial aims to detect an increase in remission (10% to 30%). An interim futility analysis will occur after 7 participants per basket reach 24 weeks.

Potential impact: Findings from this proof-of-principle study will inform the feasibility and design of future randomised trials evaluating combination biologic therapy in inflammatory arthritis.

Study registration: www.isrctn.com; ISRCTN50666516

Key words: Rheumatoid arthritis, Psoriatic arthritis, Immune-mediated inflammatory diseases, Combination biologic therapy, Tumour necrosis factor inhibitors, Interleukin-6 inhibition, Adaptive basket trial, Proof-of-principle study, Simon two-stage design, Multi-omic analysis, Multinational clinical trial

Lay summary

What does this mean for patients?

Rheumatoid arthritis and psoriatic arthritis are long-term inflammatory conditions that cause joint pain, swelling and fatigue. Current treatments for both conditions do not usually keep people better for a long time. The study aims to find out if using two treatments together (tumour necrosis factor and interleukin-6 inhibitors) works better than using just one treatment on its own. The researchers will also look at whether this approach is safe and practical to use. Learnings from this small study will help decide if a bigger, more definitive trial should be run in the future.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterised by inflammation of the joints, leading to pain, stiffness, and progressive joint damage (19). Psoriatic arthritis (PsA) is a chronic autoimmune condition characterised by inflammation of the joints, skin manifestations of psoriasis, enthesitis, dactylitis, and nail involvement (13). RA affects approximately 1% of the global population and can significantly impact the quality of life of affected individuals (43), while PsA affects up to approximately 30% of individuals with psoriasis, leading to significant morbidity and impairment of quality of life (34). Conventional therapies providing mainly symptomatic relief and slowed disease progression to some extent for RA include nonsteroidal anti-inflammatory drugs (NSAIDs) and conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) such as methotrexate (MTX), sulfasalazine, and hydroxychloroquine (31). Biological therapies have revolutionised the management of RA by specifically targeting key components of the immune system involved in the pathogenesis (24). Common biological treatments used to treat RA include tumour necrosis factor (TNF) inhibitors, interleukin-6 (IL-6) inhibitors, B-cell depletion therapy, T-cell co-stimulation blockade, and Janus kinase (JAK) inhibitors. These treatments can effectively reduce inflammation and halt joint damage in patients with moderate to severe disease who have failed conventional therapy. Similarly to RA, conventional treatment for PsA includes NSAIDs and csDMARDs, providing symptomatic relief and helping to slow disease progression in some patients (22). The advent of biological therapies has improved the management of PsA by targeting specific immune pathways implicated in its pathogenesis (24). TNF inhibitors have demonstrated efficacy in reducing joint inflammation, improving physical function, and inhibiting structural damage in patients with moderate to severe disease (26). Other biological treatments used for the treatment of PsA include IL-17 inhibitors, IL-12/23 inhibitors, and JAK inhibitors. According to the European Alliance of Associations for Rheumatology (EULAR) the target of standard care should be remission or, if remission is not possible, low disease activity (16; 44). In previous work, remission or low disease activity was only achieved in 40% of patients with RA following biological therapy (45) and 67% of patients with PsA (46), which represents a significant unmet need for improved therapeutics.

Rationale for trial

Preclinical validation at the Consorci Institut D'Investigacions Biomediques August Pi i Sunyer (IDIBAPS) demonstrated superior efficacy of combining IL-6 receptor and TNF inhibitors versus monotherapies in the Collagen-Induced Arthritis Mouse Model.

TNF inhibitors: Five TNF inhibitors (TNFi - infliximab, etanercept, adalimumab, golimumab, and certolizumab) are approved by the Food and Drug Administration in the US and European Medicines

Agency in Europe for both RA and PsA treatment for efficacy over placebo (1), for reducing radiographic progression when combined with methotrexate (29), and for arthritic and skin manifestations (36). According to UK registry data, TNFi are associated with reduced cardiovascular risk when compared to csDMARDs (25). Although TNFi are associated with an increased risk of reactivation of latent tuberculosis (4; 8; 40) and increased risk of non-melanotic skin cancers they still have the best safety profile when compared to other biological therapies (40).

IL-6 inhibitors: Tocilizumab (approved for RA in 2009) and sarilumab (approved for RA in 2017) are known to improve symptoms of RA and reduce radiographic progression (8; 23; 39), while clazakizumab can improve arthritic symptoms without a significant reduction in skin disease activity (28). Safety profiles include infection risk, with additional monitoring for neutropenia, lipids, and rare gastrointestinal perforation (39).

This trial represents the culmination of the EU Horizon 2020 funded Decision on Optimal Combinatorial Therapies in IMIDs Using Systems Approaches (DocTIS) project (https://doctis.eu), which is built on the premise that immune-mediated inflammatory diseases (IMIDs), despite their clinical differences, share some common molecular features, and that this can be exploited to achieve much-needed therapeutic advances, with sustained remission remaining elusive for many patients despite the improvement in treatment outcomes observed. The DocTIS programme analysed molecular signatures of bulk and single-cell transcriptome of peripheral blood mononuclear cells, and plasma proteomics from patients with one of five IMIDs (RA, PsA, Psoriasis, Inflammatory Bowel Disease, and Systemic Lupus Erythematosus) before and after biological treatments collected at the IMID-Biobank, Vall d'Hebron Research Institute (VHIR), Barcelona, Spain. The phenotypes of extreme responders and non-responders were identified, and systems biology analyses conducted to identify the optimal combination therapies based on patient data using a method developed by IMIDomics, Inc. and VHIR called Mitigation of Non-Response Signature (MNRS). The results showed that the combination of IL-6 and TNF inhibitors in RA patients have additive anti-inflammatory effects. Similar but smaller magnitude of benefit was observed with the combination of IL-6 and TNF inhibitor in PsA (21). These findings provide molecular evidence supporting combination therapy approaches for patients with inadequate response to monotherapy. Therefore, considering the inadequate treatment response previously reported in patients with IMIDs, there is a clear need to investigate whether the combination of biological therapies leads to a significant improvement in treatment outcomes.

Aims and objectives

The study aims to demonstrate that a clinically meaningful remission rate of 30% can be achieved using novel combinatorial therapy, compared to the 10% remission rate seen in standard care treatments, in either or both conditions.

Primary objective

The primary objective is to provide proof-of-principle validation of the potential activity of combining TNF and IL-6 inhibitors to achieve higher remission than current therapies in RA and/or PsA.

Secondary objectives

Secondary objectives are to provide preliminary safety and tolerability data on the combinatorial therapy and quantify changes in disease activity and wellbeing outcomes (QoL) as assessed using validated instruments.

METHODS

Study design

This is a multi-centre, prospective, single-arm, adaptive basket trial of a combinatorial therapy involving TNF and IL-6 inhibitors in patients with either RA or PsA. The basket design is an efficient strategy for evaluating a treatment simultaneously in multiple conditions which share common underlying disease mechanisms, as is the case with IMIDs (17). The conduct and reporting of our work has been guided by the latest published SPIRIT recommendations (7), and the ACE-CONSORT for adaptive designs will be adopted for reporting the results of our trial (12).

The Centre for Trials Research (CTR) at Cardiff University is the host institution. Ethical approval has been granted by the Health and Care Research Wales Ethics Committee (HVH EC) for the recruitment of participants from sites in the UK (8 sites) and by the Vall d'Hebron University Hospital Ethics Committee for two sites in Spain.

Eligibility

Participants with a separate and confirmed diagnosis of either RA or PsA will be recruited to the trial, with the aim of recruiting approximately 20 participants for each condition (Table 1).

Cohort and recruitment

Eligible patients with RA or PsA will be identified from upcoming patient lists of those attending rheumatology clinics. Clinicians will discuss the trial with eligible patients and provide a patient

information sheet if interest is expressed. Information about the trial is also available online (https://www.cardiff.ac.uk/centre-for-trials-research/research/studies-and-trials/view/doctis). If a patient wishes to participate then a screening visit will be arranged, written informed consent taken, and study assessments completed at screening.

Trial intervention

Patients with RA or PsA currently receiving treatment with a TNF inhibitor (etanercept, adalimumab, golimumab, certolizumab or infliximab) for ≥6 weeks, will have another biological therapy, an IL-6 inhibitor (tocilizumab or biosimilar) added to their treatment regimen whilst continuing on their TNF inhibitor. IL-6 inhibitor will be administered subcutaneously at a dose of 162 mg/fortnight for 8 weeks, which changes to weekly doses between weeks 9-24 if the therapy is well tolerated without any adverse events (AEs).

Trial procedures

Study assessments will be recorded at participating sites at the following timepoints: screening, baseline, week 6, week 12, week 18, week 24, follow-up visit 1 (within 2-4 weeks after end of treatment), and follow-up visit 2 (within 8-10 weeks after end of treatment). See Table 2 for trial timeline.

Patient and public involvement

Patient and public involvement (PPI) was responsible for reviewing the protocol, participant information sheet and consent form.

Primary outcome measure

The primary outcome is whether patients achieve disease remission at week 24, as defined by the following criteria:

- RA - Clinical Disease Activity Index (CDAI) score of ≤2.8 (2)
- PsA - Disease Activity in PSoriatic Arthritis (DAPSA) score of ≤4 (38)

Secondary outcome measures

- Safety and tolerability outcomes will include the total number of serious adverse events (SAEs), adverse events (AEs), and adverse events of special interest (AESIs), such as severe infections requiring hospitalisation. These will be reported due to their potential impact on patient health

outcomes and the overall safety profile of the treatment. Withdrawals related to SAEs, AEs, or AESIs will also be summarised.

- Disease activity: For RA: CDAI (2); for PsA: DAPSA (38); for both: pain assessed by Visual Analogue Scale (VAS) (3), patient global assessment (6), physician global assessment (5), physical functioning assessed by modified Health Assessment Questionnaire (mHAQ) (27), and C-reactive protein (CRP).
- Psychological health and wellbeing: For RA: Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAF-MDQ) (30), Rheumatoid Arthritis Impact of Disease (RAID) (15); for PsA: Psoriatic Arthritis Impact of Disease-9 items (PsAID-9) (14); for both: Short Form-12 items (20).
- Cardiometabolic status: Assessments by physical examination (body mass, blood pressure, and heart rate measurements).

See Table 2 for trial assessments and timeline.

Safety reporting

The safety and tolerability of the combination therapy will be assessed up to 10 weeks following the end of treatment (see Table 2 for trial assessments and timeline). Comorbid conditions are common in our cohort with inflammatory arthritis (42), and given the association between SAEs and the biological treatments taken by this group (11), the monitoring of expected events such as AEs and hospitalisations is warranted as part of the trial data collection. Sites will report all SAEs that occur to the CTR pharmacovigilance and safety specialist within 24-hours of knowledge of the event, and the safety issue will be followed up until completion. All SAEs will be reviewed by the principal investigator or a delegated clinician at the site, and by the Chief Investigator or a delegated clinician within the Trial Management Group (TMG) to determine the causal relationship between the event and treatment. Additionally, SAEs will be sent to the Independent Data Monitoring Committee (IDMC) for review.

Statistical analysis

Sample size

The sample size calculation is based on the primary outcome i.e. the proportion of patients who achieve disease remission at week 24. Within each disease basket (RA and PsA), the aim is to demonstrate a clinically worthwhile increase in the remission rate from an assumed 10% under current standard care conditions to 30% using the novel combinatorial therapy. To do so in a Simon's two-stage design with 80% power and one-sided 10% type I error rate, as is appropriate for a phase II

study, 18 patients with evaluable primary outcome data will be required per basket i.e. 36 in total. This corresponds to both the optimal (i.e. minimising the expected sample size) and minimax (i.e. minimising the maximum sample size) Simon's two-stage design (41). Assuming 10% loss to follow-up at week 24, the overall recruitment target is 40.

Interim analysis

An interim analysis will be performed separately for each basket after 7 participants have provided primary outcome data. As per the Simon's two-stage design, if not a single participant has achieved remission at 24 weeks, recruitment to that basket will be stopped for futility. Depending on the pace of recruitment it is possible that by the time the 7th participant in a basket has completed their 24-week follow-up, the maximum sample size of 20 has already been recruited for that basket. In that case, the interim analysis cannot inform early stopping of recruitment, but it can still provide patient benefit by allowing to stop the administration of the combination therapy if it is unlikely to be efficacious, and answer the research question sooner.

Main analysis

A detailed analysis plan will be signed off prior to any analysis being performed. Participants' baseline characteristics will be summarised by basket using appropriate descriptive statistics such as means and standard deviations or medians and interquartile ranges for continuous variables, and frequencies and percentages for discrete variables.

Primary outcome analysis

The primary analysis will include all participants providing primary outcome data regardless of their level of adherence to the treatment regimen, and be performed separately for each basket using Simon's two-stage design criteria: if ≥3 out of 18 participants achieve remission at 24 weeks, the combination therapy will be declared successful for that basket. Two-sided 80% confidence intervals (corresponding to the one-sided 10% type I error rate) for remission rates will be calculated using exact binomial methods. Continuous measures of the secondary outcomes (e.g. CDAI, DAPSA, mHAQ scores) will be summarised by basket using means and standard deviations, or medians and interquartile ranges, at each time point. Categorical measures (e.g. response rates, AE frequencies) will be summarised by basket using frequencies and percentages at each time point. Paired t-tests and McNemar's tests will be used for within-group comparisons against baseline, where appropriate. All estimates will be presented along with their two-sided 80% CI. Additionally, bias-adjusted estimates and CIs accounting for the adaptive design will be reported (32).

Additional analysis

If both baskets continue to the main analysis, we will consider additional exploratory pooled analyses where information is borrowed across baskets. Three methods will be used to pool the results of the two baskets; a Bayesian hierarchical model (BHM), a calibrated BHM, and Bayesian model averaging (9). The aim of this analysis will be to explore potential similarities and differences between RA and PsA, and not to draw confirmatory conclusions.

Sensitivity analysis and missing data

A sensitivity analysis will be conducted estimating the treatment effect only among participants who adhered to their treatment regimen. Adherence will be recorded using the ABC taxonomy (47): initiation (first dose taken), implementation (dosing consistency), and discontinuation (time of last dose). Adherence rates will be calculated as the proportion of prescribed doses taken and summarised by basket. The amount of missing outcome data will be tabulated by variable, basket, and time point.

Trial management

The trial is sponsored by Cardiff University (SPON2002-24), coordinated by the CTR, and conducted with Vall d'Hebron Research Institute as a partner organisation.

Data management

All trial data collected at participating sites will be entered directly into a secure database built using the Research Electronic Data Capture (REDCap) system following trial visits (35), including data collected from patient-reported outcome measures onto paper forms (18). All data captured on REDCap will be stored on a secure server hosted by Cardiff University. The REDCap database is accessed by an individual username and password. Upon adding a new record, the REDCap database will automatically assign the participant with a unique identifier in a sequential order for each site. Participants will only be known by this identifier when using REDCap. To protect the identity of participants and minimise risk of information breaches, data access groups will be created in REDCap to ensure that trial staff signed onto the delegation log can only view data collected at their own site. Furthermore, all identifiable fields will be tagged e.g. date of birth, to enable electronic data to be exported from REDCap in a de-identified format.

In accordance with the approved trial data management plan and CTR policies, a 10% proportion of paper forms collected will be quality checked to ensure the responses on the paper form match the

data entered into the REDCap database. The sites will send electronic scans of the paper forms to the CTR via Fastfile (https://fastfile.cardiff.ac.uk/), a secure repository hosted by Cardiff University for sharing files. Any errors identified during the check will be corrected. Following trial completion, data will be archived for 15 years in accordance with CTR policies.

Trial Management Group

The Trial Management Group (TMG) will convene every 1-2 months, which will change to every 3 months following study set-up of all sites until study closure with the aim of managing all practical, clinical, and administrative aspects of the trial. This entails providing input into the development or refinement of all data collection tools and trial documentation, ensuring the trial is delivered as outlined in the protocol, providing guidance to resolve trial queries and monitor adverse events that occur, considering any recommendations made by the IDMC throughout the trial, and assisting with the production and dissemination of trial publications and reports. The TMG consists of the Chief Investigator, Co-Investigators, Statisticians, Trial Managers, Data Managers, Trial Administrator, Safety Representative, Sponsor Representative, site PIs and DocTIS Coordinator. All TMG members will be required to sign the TMG charter outlining the trial conditions.

Trial Steering Committee

A Trial Steering Committee (TSC) is independent of the trial and TMG and will monitor trial progress in an advisory capacity, and report to the trial funder and sponsor (10). In DocTIS, this role is fulfilled by the members of the IDMC.

Independent Data Monitoring Committee

An IDMC will review interim trial data to maintain data integrity and ensure participant safety, providing recommendations directly to the TMG and/or sponsor on whether to modify aspects of the trial and continue/discontinue participation (37). Members of the IDMC will meet at least annually and sign the IDMC charter clarifying the remit of the group.

Ethics and dissemination

Research ethics approval

This protocol has approval from Wales Research Ethics Committee 1 that is legally recognised by the United Kingdom Ethics Committee Authority and by the Spanish Vall d'Hebron University Hospital Ethics Committee for review and approval.

Protocol amendments

This trial protocol has been submitted through the relevant permission system for global governance review dependant on the location of the lead site e.g. Health and Care Research Wales (HCRW) or the Health Research Authority (HRA), and Vall d'Hebron University Hospital Ethics Committee.

This trial has Clinical Trials Authorisation (CTA) from the UK Competent Authority, MHRA. The process for making amendments to the protocol and other key trial documents will follow relevant CTR standard operating procedures. All amendments will be undertaken in agreement with the TMG.

Key amended trial documents, and a summary of their impact on trial processes, will be provided to all participating centres in a timely manner and updated approvals gathered from sites as required.

Consent

A participant's written informed consent must be obtained using the trial consent form, which follows the participant information sheet. The participant should be given sufficient time after the initial invitation to participate before being asked to sign the consent form. Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial. Consent may be taken by the principal investigator or delegated staff at site.

Confidentiality

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified. Data will be stored in a secure manner and will be registered in accordance with current, relevant regulations.

Ancillary and post-trial care

There will be two follow-up phone calls with the patient to capture any late effects of the combination therapy. These take place at 2-4 weeks after the end of treatment and 8-10 weeks after the end of treatment.

Dissemination policy

Trial results will be disseminated through scientific publications and conference presentations. A detailed publication plan including specific authorship eligibility guidelines will be developed and agreed upon by the TMG.

DISCUSSION

This protocol paper describes a proof-of-principle study designed to examine the potential activity of TNF and IL-6 inhibitor combination therapy in patients with active RA or PsA despite current biologic treatment, addressing an unmet care need for patients with RA or PsA as only 40% and 67% respectively achieve remission with current therapies. This study is designed to provide preliminary evidence to support or refute further investigation of this combinatorial approach.

Evidence from the DocTIS programme's multi-omic analysis and preclinical validation in mouse models are used as the basis of this trial, showing early promise that combining TNF and IL-6 inhibitors could have complementary effects on patients. Some of the trial's strengths are its solid scientific background, the comprehensive safety reporting, and the utilisation of an efficient adaptive basket design, allowing for the evaluation of the combination therapy in both RA and PsA simultaneously, with early stopping for futility if indicated and the potential to 'borrow' information across disease baskets at the final analysis. Exploratory analysis borrowing information across disease baskets will be conducted using Bayesian hierarchical modelling approaches, in order to explore potential similarities and differences between the two baskets. Pooled estimates will be interpreted with caution, taking into account the limited sample size and the potential heterogeneity between baskets. However, the small sample size and the fact that no comparison group is included may limit the generalisability of the results. Despite these limitations, if the DocTIS trial offers encouraging outcomes and the combinatorial approach is well tolerated, the results could provide the foundation for larger randomised controlled trials. Such studies would be necessary to establish definitive evidence for this combination therapy approach and potentially inform future treatment guidelines for patients with refractory RA and PsA.

Strengths and limitations of this study

- Design strength – Rationale for trial: This protocol describes a proof-of-principle study designed to address an unmet clinical need as remission rates remain low in rheumatoid arthritis (~40%) and psoriatic arthritis (~67%) despite biologic treatment.
- Design strength – Scientific basis: Strong preclinical basis from DocTIS multi-omic data suggesting complementary effects of tumour necrosis factor + interleukin-6 inhibition.
- Design strength – Methodology: Adaptive basket design, including early stopping for futility with the potential of combining baskets and borrowing information between rheumatoid and psoriatic arthritis.
- Anticipated limitation – Sample size: Small sample size and the absence of a control group may limit generalisability.

- Anticipated limitation – Preliminary findings: Larger randomised controlled trials will be required to establish efficacy and safety.

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Conflict of interest: The authors declare that they have no conflicts of interest.

Ethics statement: The study was approved by the Wales Research Ethics Committee 1 (24/WA/0336) and Vall d'Hebron University Hospital Ethics Committee (AC/M(AG)044/2025(6529)).

Data availability: Requests to obtain trial data will be granted at the discretion of the Centre for Trials Research (CTR) at Cardiff University, following the submission of a clear and scientifically justified rationale for using the trial data as per the CTR policy on data sharing.

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Tables

Table 1: Trial eligibility criteria

Inclusion criteria	Exclusion criteria
• Patients aged ≥18 years.	• Contraindications to any biologic treatment.
	• Previous treatment with any IL-6 inhibitors e.g. tocilizumab, sarilumab.
• Patients must fulfil either EULAR/ACR classification criteria for the diagnosis of RA, or CASPAR criteria for PsA.	• Women who are pregnant or breast-feeding.
	• Women of child-bearing potential, or males with a female partner of child-bearing potential, refusing to use effective contraception throughout the trial and for at least 3 months after stopping trial treatment.
	• Previous history of, or current primary inflammatory joint disease or primary autoimmune disease other than RA.
• Receiving treatment with any approved TNF inhibitors.	• Intra-articular or parenteral corticosteroids ≤4 weeks prior to visit 2.
	• Oral prednisolone >10mg/day or equivalent ≤4 weeks prior to visit 2.
	• Active infection.
	• Septic arthritis within a native joint within the last year.
• Active arthritis as defined by: RA – DAS28 score ≥3.2 PsA – DAPSA score >14	• Sepsis of a prosthetic joint within the last year or indefinitely if the joint remains in situ.
	• Known HIV or hepatitis B/C infection (satisfactory hepatitis B screening test must have been done previously).
• Written informed consent.	• Malignancy within the last decade (other than basal cell carcinoma).
	• New York Heart Association class III or IV congestive cardiac failure.
	• Demyelinating disease.

Abbreviations: ACR = American College of Rheumatology; CASPAR = Classification for Psoriatic Arthritis; DAPSA = Disease Activity in Psoriatic Arthritis; DAS28 = Disease Activity Score 28-joints; EULAR = European Alliance of Associations for Rheumatology; HIV = Human Immunodeficiency Virus; IL = Interleukin; PsA = Psoriatic Arthritis; RA = Rheumatoid Arthritis; TNF = Tumour Necrosis Factor.

Table 2: Trial assessments and timeline

Participant assessments	Timeline							
	Pre-intervention period		24-week intervention period				Follow-up period	
	Screening	Baseline	6wk	12wk	18wk	24wk	FU1 (2-4 wk after treatment)	FU2 (8-10 wk after treatment)
Screening	X							
Medical history	X							
Consent	X							
Demographics	X							
Concomitant medications	X	X	X	X	X	X		
Corticosteroid therapy	X							
Physical examination (vital signs)	X	X		X		X		
Assessments by VAS (0-10cm)	X	X		X		X		
Physical functioning (mHAQ)	X	X		X		X		
CDAI (RA)	X	X		X		X		
DAPSA (PsA)	X	X		X		X		
Screening bloods (rheumatoid factor, anti-CCP antibodies, and lipid profile)	X							
Routine bloods (FBC, U&E, LFT, ESR, and CRP)	X	X	X	X	X	X		
Trial blood collection (PAXgene blood RNA and EDTA tubes)		X				X		
Disease impact (RA: BRAF-MDQ, SF-12, and RAID)		X				X		
Disease impact (PsA: SF-12 and PsAID-9)		X				X		
Trial drug adherence		X				X		
Adverse event assessment		X	X	X	X	X	X	X
Death	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
Withdrawal	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]

Abbreviations: BRAF-MDQ = Bristol Rheumatoid Arthritis Fatigue MultiDimensional Questionnaire; CCP = Cyclic citrullinated peptide; CDAI = Clinical Disease Activity Index; CRP = C-reactive protein; DAPSA = Disease Activity in Psoriatic Arthritis; EDTA = Ethylenediaminetetraacetic acid; ESR = Erythrocyte sedimentation rate; FBC = Full blood count; FU = Follow-up; HIV = Human Immunodeficiency Virus; mHAQ = modified Health Assessment Questionnaire; LFT = Liver function test; PsA = Psoriatic Arthritis; PSAID-9 = Psoriatic Arthritis Impact of Disease-9 items; RA = Rheumatoid Arthritis; RAID = Rheumatoid Arthritis Impact of Disease; RNA = Ribonucleic acid; SF-12 = Short Form-12 items; U&E = Urea and electrolytes; VAS = Visual Analogue Scale; Wk = Week. [1]Form is only completed if required at any timepoint.