Clinical and ultrasonographic predictors for achieving minimal disease activity in patients with psoriatic arthritis: the UPSTREAM (Ultrasound in PSoriatic arthritis TREAtMent) prospective observational study protocol

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ABSTRACT

Introduction Psoriatic arthritis (PsA) occurs in 10%–15% of people with psoriasis and accounts for 10%–20% of early arthritis clinics referral. Only a few prognostic factors of therapeutic response in patients with PsA have been identified. In the last years, the role of imaging has grown up and the European League Against Rheumatism recognised that ultrasound (US) has higher sensitivity than clinical examination to detect inflammatory disease activity. The aims of the Ultrasound in Psoriatic arthritis TREAtMent (UPSTREAM) study are to integrate clinic and US in order to inform whether US has provide an added prognostic value in PsA.

Methods and analysis UPSTREAM is an observational prospective cohort study enrolling patients with PsA having clinically active joint disease and starting a new course of therapy. The primary objective is to evaluate the additional value of US over clinical examination in detecting patients achieving minimal disease activity after 6 months. Data will be obtained at baseline and at standard clinical follow-up visits. Patient’s clinical assessment will be performed according to the core set proposed by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis-Outcome Measures in Rheumatology. Sonographic evaluations will be performed by expert sonographers in 42 joints, 36 tendons, 12 entheses and 2 bursae, according to a score that will be purposely developed for PsA by the US Study Group of the Italian Society for Rheumatology. The UPSTREAM study will identify clinical and US predictors of response to treatment in patients with PsA and active peripheral arthritis starting a new course of therapy.

Ethics and dissemination Ethic approval for this study has been obtained from the institutional review board (IRB)/independent ethics committee (IEC) Comitato Etico Lazio 1 (Prot. N 198 02-02-2017) and then locally from the IRB/IEC of each participating centre. Results will be published in relevant scientific journals and be disseminated in international conferences. Fully anonymised data will be accessible from authors upon request.

Strengths and limitations of this study

- Ultrasound in Psoriatic arthritis TREAtMent (UPSTREAM) is a large prospective multicentre cohort study aiming to investigate predictors of treatment response in patients with active psoriatic arthritis receiving a new course of therapy; it especially focus on the potential role of musculoskeletal ultrasonography (US).
- UPSTREAM US evaluations will be performed by sonographers blind to clinical data, and the choice of treatment (ie, change or step up of therapy) will be independent by US results.
- In order to enhance validity and reliability of the UPSTREAM study results, sonographers will be provided with a reference atlas and they will be selected based on local availability of a high-level US machine and high-reliability exercise scores (kappa statistics value ≥0.7 compared with a ‘gold-standard’ scorer) on US static images.
- The UPSTREAM study is designed to minimise the potential risk of selection bias associated with observational studies but, as the participation is voluntary, an attrition bias(maximum expected 20%) cannot be excluded.
- UPSTREAM study population is heterogeneous for disease duration, type of articular involvement and therapy; giving the opportunity for a stratification of the predictors but, at the same time, it could be a limitation for identification of general predictors of minimal disease activity.

Trial registration number NCT03330769; Pre-results.

INTRODUCTION

Psoriatic arthritis (PsA) is a potentially disabling chronic inflammatory disease with articular and extra-articular features. To date, remission is considered the ultimate goal of...
therapy in PsA, even though it could be difficult to achieve and to maintain, thus a minimal disease activity (MDA) is considered an acceptable target.\(^1\)\(^2\) In view of the therapeutic target of remission or MDA, the identification of adverse prognostic factors and the best treatment strategy are two important items in research agenda of PsA.\(^2\)

Currently, only a limited number of observational and prospective cohort studies have identified prognostic factors associated with therapeutic response in patients with PsA. Recently, Eder et al demonstrated that overweight and obesity, female gender, old age and a longer duration of the disease were associated with a lower probability of achieving sustained MDA.\(^3\) Furthermore, the Swedish early PsA register demonstrated that a shorter delay between the onset of symptoms and diagnosis was a predictor for MDA.\(^4\) Moreover, low Health Assessment Questionnaire (HAQ) at baseline was associated with a better response in PsA.\(^5\)\(^6\) Recently a treat-to-target (T2T) strategy aimed to investigate the effect of tight control on early PsA showed an effect (OR 1.91, 95% CI 1.03 to 3.55; \(p=0.039\)) in improving the therapeutic response measured by the American College of Rheumatology (ACR) 20% (ACR20) at 48 weeks.\(^7\) However, radiographic progression did not differ in the various strategies whereas more adverse events (AEs) with higher costs were registered in the tight control group. Undoubtedly, the T2T strategy in PsA needs further evidence before it can be successfully applied. The main challenges in applying the T2T strategy in PsA are related to the lack of major predictors of therapeutic response and to the wide heterogeneity of the disease, including both axial and peripheral involvement and specific additional features (ie, dactylitis, enthesis) as well as extra-articular manifestations, which activity it is not fully captured by the available composite indices.\(^8\)\(^9\) An intriguing prospective is to identify ultrasonographic predictors of therapeutic response in PsA and to integrate clinical examination with musculoskeletal ultrasonography (US) in order to stratify patients according to the prognostic factors and to establish treatment in a T2T strategy. In the last years, the role of imaging in spondyloarthritis (SpA) is grown and the European League Against Rheumatism recommendations recognised that US has higher sensitivity than clinical examination in detecting signs of disease activity and peripheral enthesitis to support the diagnosis of SpA.\(^10\)\(^11\) However, the utility of US in PsA is not supported by sufficient evidence yet and integrating imaging in routine clinical practice is still a challenge of the next future.\(^12\) In this context, it is crucial to identify an US composite score that could explore all the domains of the disease in a feasible manner, especially in the typically polymorphic aspects of PsA. In 2012, Gutierrez et al developed a power Doppler (PD) composite score focused on joints, tendons, entheses, skin and nails, aiming to define the overall disease activity.\(^13\)\(^14\) More recently, Ficjan et al developed two new US composite scores (PsASon-13 and PsASon-22), derived from a total US score (68 joints/14 enthesis) in order to have a high sensitivity to detect PsA features and a good feasibility in clinical practice.\(^14\) However, none of the simplified scores produced have been validated so far in terms of content, construct and criterion validity.

In this scenario, the UPSTREAM (Ultrason in PSo-riatic arthritis TREATMent) study will represent the first clear example of integration between the clinic and US in PsA and it will generate evidence to inform whether US could be an added prognostic value responding to the need of tailoring treatment that would allow clinicians to practice a more effective and personalised medicine, optimising the outcomes of patients with PsA as well as the treatment management.

### METHODS AND ANALYSIS

#### Study aims

The aims of the UPSTREAM study are to identify clinical and US predictors of achieving MDA, remission, better imaging and functional outcomes in clinically diagnosed PsA with active peripheral arthritis starting a new course of therapy (box 1). The analysis of ultrasonographic data will develop a score (PsA-SIR US-score) to be used as a prognostic indicator of treatment response and two subscores: one related to disease activity (PsA-SIR US inflammatory subscore) and the other related to disease damage (PsA-SIR US damage subscore).

#### Primary objective

To evaluate the additional value of US (PsA-SIR US-score) over clinical examination in predicting MDA\(^15\) at 6 months in patients with PsA with clinically active joint disease starting a new course of therapy.

#### Secondary objectives

In clinically diagnosed PsA with clinically active joint disease starting a new course of therapy:

- To evaluate the additional value of US over clinical examination in detecting patients:

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**Box 1 Inclusion criteria for participants**

**Inclusion criteria**

- Adult >18 years of age with psoriatic arthritis according to the Classification Criteria for Psoriatic Arthritis (CASPAR).
- At least one joint clinically involved (both swelling and tenderness).
- Not satisfying the minimal disease activity criteria at baseline.
- Prescription of new course of NSAIDs (monotherapy), steroid intra-articular injections (monotherapy), csDMARDs, bDMARDs, tsDMARDs, including switches or dose augmentations indicated by the treating rheumatologist according to usual clinical practice before ultrasound acquisition.
- Stable dose of medications for at least 6 weeks before prescription of new course of treatment.
- The patient must be able to adhere to the study visit schedule and other protocol requirements.
- csDMARDs, conventional synthetic disease modifying antirheumatic drugs; bDMARDs, biologic disease modifying antirheumatic drugs; tsDMARDs, targeted synthetic disease modifying antirheumatic drugs; NSAIDS, nonsteroidal anti-inflammatory drugs.
- Achieving MDA at 12 months (including sustained).  
- Achieving Disease Activity Index for Psoriatic Arthritis (DAPSA) remission at 6 and 12 months (including sustained).  
- Achieving ACR remission at 6 and 12 months (including sustained).  
- With X-ray structural progression using the modified Sharp-van der Heijde score (mSVH score) at 12 and 24 months.  
- With US structural progression (US-damage score) at 12 and 24 months.  
- With functional worsening using the HAQ (deltaHAQ) at 12 and 24 months.  
- With impairment of health-related quality of life (HRQoL) at 12 and 24 months.

To explore whether clinically detected disease activity due to joint tenderness without swelling is related to joint or extra-articular US-detected inflammation evaluated by US.

To explore clinical features and US-lesions related to X-ray detected bony apposition.

**Study design**

UPSTREAM is a 24-month multicentre observational prospective cohort study of at least 250 patients affected with PsA. The study, V.1.3, 28-11-2016, is registered at ClinicalTrial.gov (NCT03330769) at "pre-results" stage.

**Patient and public involvement**

Patients and or public are not involved in design, recruitment and conduct of the study.

**Recruitment (patient selection, inclusion and exclusion criteria)**

Eligible patients will be identified from rheumatology clinics at 40 sites in Italy. A study initiation meeting will provide full training in clinical and ultrasonographic study procedures to at least one investigator per centre who will fully train local collaborators in the study.

Patients with diagnosis of PsA according to CASPAR criteria and starting a new course of therapy for clinically active joint disease will be recruited. Eligibility for the study will be determined at a clinical screening visit with a rheumatologist. The study team will ensure that the patient satisfies the study inclusion criteria listed in box 1. An institutional review board (IRB)/independent ethics committee (IEC) will review and approve the protocol and informed consent form before any subject is enrolled at rheumatology centre (online supplementary file).

Before any protocol-required procedures are performed, the subject must sign and date the IRB/IEC-approved informed consent form.

**Procedures and scheduled follow-up visits**

Patients recruited in the UPSTREAM study will be seen at 3, 6, 12 and 24 months after baseline (table 1). Baseline and each follow-up visit will entail a physical examination, a full clinical disease assessment, concomitant and medical history, obtaining of safety and efficacy bloods. US assessments will be performed at baseline and after 6, 12 and 24 months. Clinical assessments will be performed by a rheumatologist (clinical assessor) blind to US data. US evaluations will be performed by a rheumatologist (sonographer) blind to clinical data.

Each patient considered eligible for the study will be classified according to predominat clinical subset(s) of PsA: (1) monoarticular or asymmetric oligoarthritis with or without dactylitis; (2) symmetric polyarthritis similar to rheumatoid arthritis; (3) classic PsA confined to distal interphalangeal joints of hands and feet; (4) spondylitis with or without peripheral joint involvement and (5) arthritis mutilans. The demographic variables age, sex, ethnic group, family history, body weight, height and smoking habit will be recorded. On enrolment in the study, a detailed medical history will be recorded mostly focusing on PsA (onset of symptoms, date of diagnosis), related treatment (current and previous medication, reason for withdrawal) and associated comorbidities (eg, SpA spectrum comorbidities). To assess comorbidities, disease-specific recommendations will be followed.

To increase feasibility and reliability, metabolic syndrome will be defined as follows: (1) body mass index >30 kg/m²; (2) a diagnosis of type 2 diabetes mellitus and (3) a diagnosis of hypertension.

**Clinical assessment**

**Methods of assessment**

Patient’s assessment will be performed according to the core set of domains for PsA proposed by the Group for Research and Assessment of Psoriasis (GRAPPA) and Psoriatic Arthritis and Outcome Measures in Rheumatology (OMERACT). Assessment of peripheral joint activity will be performed using the 68-tender joint count (TJC) and the 66-swollen joint count (SJC). Positive joints will be recorded and the total number of tender and swollen joints will be calculated. Intraclass correlation coefficient (ICC) for TJC in the patients with PsA was 0.78 (95% CI 0.61 to 0.93) and for SJC was 0.50 (95% CI 0.27 to 0.78). Enthesitis is characterised by inflammation at sites of tendon, ligament and joint capsule fibre insertion into bone, and is considered a pathophysiologically important aspect of PsA. For the purpose of the UPSTREAM study, enthesitis will be assessed using: the Leeds Enthesitis Index (ICC 0.81; 95% CI 0.63 to 0.94), an enthesitis index specifically developed for PsA, and four additional bilateral enthesal sites (quadriiceps insertion patella, plantar fascia, inferior pole patella, ...

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tibial tubercle). Dactylitis will be evaluated using the tender dactylitis count on 20 digits; the clinician squeezes the swollen fingers with moderate pressure and documents the patient’s response.23 Spinal assessment will be performed using the Bath Ankylosing Spondylitis Disease Activity Index,25 a set of six Visual Analogue Scale (VAS) scores patient questionnaires regarding fatigue, pain and stiffness (ICC 0.89).22

Patient global assessment (PtGA), patient pain assessment (PtA of pain) and physician global assessment will be assessed by a 0–100 VAS.23

Cutaneous psoriatic lesion burden will be assessed using the body surface area (BSA) method which consider the surface area of the patient’s handprint (palm and fingers) as representing 1% of the BSA.26

Physical function will be assessed using the HAQ. Any subject rate the degree of difficulty they have had in the past week on a 4-point scale, ranging from 0 (no difficulty) to 3 (unable to do).17 The HRQoL domain will be assessed using the Psoriatic Arthritis Impact of Disease 12-item (PsAiD-12) questionnaire, which includes 12 domains each assessed by a single question with response on a NRS between 0 and 10 where higher numbers indicate worse status. PsAiD-12 minimal clinically important improvement was found to be three points.27 Reliability of the PsAiD-12 Italian version calculated by Cronbach’s alpha coefficient was 0.93.28

### Table 1

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ACPA, anti-citrullinated protein antibodies; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C reactive protein; ESR, erythocyte sedimentation rate; HAQ, Health Assessment Questionnaire; HLA, Human Leucocyte Antigen; PsAiD-12, Psoriatic Arthritis Impact of Disease 12-item; PsA-SIR, psoriatic arthritis—Society of Rheumatology; RF, Rheimatoid Factor; VAS, Visual Analogue Scale.
Blood tests will be performed locally. Erythrocyte sedimentation rate and C reactive protein will be determined at each protocol time point and collected along with reference ranges.

**Safety monitoring**

An AE will be defined as any untoward medical occurrence, including abnormal laboratory findings, symptoms or diseases, in a subject after providing written informed consent for participation in the study.

**US assessment**

**US articular elementary lesions**

Sonographic evaluations will be performed by expert sonographers on the same day of clinical assessment and must invariably be performed after the clinical decision to change the patient’s treatment. Furthermore, results of ultrasonographic evaluation should not be taken into account for the choice of treatment.

Grey scale (GS) and PD sonography will be performed, using a high standard US machine and multifrequency linear transducers (high-frequency probe at least 14 MHz), in 42 joints, 36 tendons, 12 entheses and 2 bursae.29

> GS-Synovitis will be evaluated by including its two components (ie, joint effusion and synovial membrane hypertrophy), which will be assessed according to the OMERACT definitions.30 In GS, the two components of synovitis (ie, joint effusion and synovial hypertrophy) will be scored together according to a 4-point semiquantitative assessment as follows: synovitis: grade 0=no synovitis; grade 1=minimal synovitis (below or at the level of bony joint line); grade 2=moderate synovitis (above level of bony joint line but without full distension of joint capsule); grade 3=severe synovitis (above level of bony joint line with distension of joint capsule which will appear convex).31 32

> PD-Synovitis will be scored by using a semiquantitative 4-point scale, as follows: grade 0=no flow within the synovium; grade 1=up to three single spots signals or up to two confluent spots signals or one confluent spot + up to two single spots signals; grade 2=PD signals covering less than 50% of the area of the synovium; grade 3=PD signals in more than 50% of the area of the synovium.33

Erosions will be defined as intra-articular discontinuity of the bone surface that is visible in two perpendicular planes.34

**US entheseal and soft tissue elementary lesions**

> Enthesitis will be defined in accordance with the recently published OMERACT definitions35 and the registered elementary lesions will be: hypoechogeticity of the enthesis (hypoechoic tendon with loss of the normal fibrillar pattern); increased thickness of tendon at its insertion; enthesophyte (a step up bony prominence at the end of the normal bone contour); calcifications; bone erosion at the enthesis; PD activity at enthesis <2 mm from the bone insertion.

> In the absence of a definition of the US bone proliferation in PsA, the OMERACT definition of osteophyte (osteoproliferation at the joint margins) will be used.36

> The presence of peritenon extensor tendon inflammation will be investigated by dorsal scans at the level of all fingers of both hands. This abnormality will be defined as a hypoechoic swelling of the soft-tissues surrounding the extensor digitotum tendons, with or without peritendinous PD signal.37 38

> Bursitis will be defined as an abnormal distension of the bursal wall,39 due to local effusion and/or synovial proliferation. PD signal will be evaluated as present/absent. The presence of mild distension of the bursal wall exclusively due to local effusion, as it can be shown in healthy subjects will be considered normal.

> Tenosynovitis will be defined on GS as abnormal anechoic and/or hypoechoic (relative to tendon fibres) tendon sheath widening which can be related to both the presence of tenosynovial abnormal fluid and/or hypertrophy. On GS, tenosynovitis will be graded according to a four-point semiquantitative scoring system as follows: grade 0=normal; grade 1=minimal; grade 2=moderate; grade 3=severe. Both longitudinal and transverse planes will be performed in order to confirm the findings.40

> On PD, tenosynovitis will be defined as the presence of peritendinous Doppler signal within the synovial sheath, seen in two perpendicular planes, excluding normal feeding vessels (ie, vessels at the mesotenon or vinculae or vessels entering the synovial sheath from surrounding tissues) only if the tendon shows peritendinous synovial sheath widening on B-mode. A four-grade semiquantitative scoring system (ie, grade 0, no Doppler signal; grade 1, minimal; grade 2, moderate; grade 3, severe) can be used to score pathological peritendinous Doppler signal within the synovial sheath.40 If, in addition to an abnormal signal detected within the sheath, an abnormal intratendinous signal will be seen in two perpendicular planes, then 1 point will be added to grades 1 and 2 (intrasynovial small isolated signals due to normal feeding vessels should be excluded).

> Tendon damage will be defined on GS as internal and/or peripheral focal tendon defect (ie, absence of fibres) in the region enclosed by tendon sheath, seen in two perpendicular planes. The grade of tendon damage should be assessed in both longitudinal and transverse planes.41

> The overall PsA-SIR US score will be calculated as a weighted sum of the scores of every lesion at all sites; in addition the inflammatory and the damage subscore will be evaluated and correlated to the outcomes of the study. Weight will be estimated in a pilot substudy on 100 patients with active PsA using a principal component analysis approach.
Radiographic assessment
Posterior–anterior radiographic assessments of wrists, hands and feet will be centrally scored at a subsequent time point by two radiologists using the mSVH score.45 The scoring will be performed pairwise, blinded to the sequence of the films and to the clinical data. Mean of two investigators will be taken as the final score for X-ray assessments.

Study outcomes
The primary endpoint of the study is achievement of MDA at 6 months. Patients with PsA will be placed in MDA when they meet five of seven of the following criteria: (1) 68 TJC ≤1, (2) 66 SJC ≤1, (3) BSA ≤3, (4) enthesitis count ≤1, (5) PtGA VAS ≤20, (6) PtA of pain VAS ≤15, and (7) HAQ ≤0.5. Secondary endpoints are achievement of MDA at 12 months, DAPSA remission (score <4) and ACR remission at 6 and 12 months including sustained outcomes. Additional secondary endpoints are functional worsening by HAQ and impairment of HRQoL by PSAID-12 at 12 and 24 months. Imaging secondary endpoints at 12 and 24 months are X-ray structural progression using the mSVH score, US structural progression using the PsA-SIR US damage subscore and the relationship between time-integrated US-detected inflammation (PsA-SIR US inflammation subscore) and US-detected damage (PsA-SIR US damage subscore).

Centre selection
All the SIR members will be invited to participate to the UPSTREAM study. In order to increase the validity and reliability of the results, the participants will be selected based on three prerequisites: (1) local availability of a high-level US machine including high-level US probes (>14 MHz); (2) reliability exercise on static images with a kappa statistics value ≥0.7 compared with a ‘gold-standard’ scorer; (3) quality assessment of US images of PsA lesions. A total of 30 static images per US-lesion type (synovitis, enthesitis, tenosynovitis, erosion, bony apposition) with 50% of them showing presence of lesions will be submitted to scoring through an online electronic platform. A reference atlas will be provided to the sonographer investigators before the exercise.

Sample size calculation
The sample size calculation was done minimising the number of false positives (ie, the number of false non-responsive to treatment) in order to minimise the risk of overtreating patients who actually have a good response to therapy. Therefore, sample size was calculated to minimise this risk by 40% (null hypothesis H0) to 20% (alternative hypothesis H1), maintaining stable at 70% (both for the H0 for both the H1), the percentage of true positives (true unresponsive to therapy).

The simulations were carried out using the Stata procedure rocsignificance (by M. Pepe), which allows to determine the power to detect an improvement in the receiver operating characteristic (ROC) curve. The procedure requires that the percentage of false and true positives are specified for both the null and the alternative hypothesis and also the percentage of diseased.

Using the command rocsignificance 0.7 0.2, na (150) ndb (100) tpnull (0.7) fpnull (0.4) of Stata, it results that 250 patients are sufficient to evaluate the performance of a model (and its ROC curve) with over 90% of power (setting a 5% alpha). Specifically, we have assumed a 70% and a 20% of subjects true positives and false positives, respectively, according to the alternative hypothesis, a 70% and a 40% of subjects true positives and false positives, respectively, according to the null hypothesis, and a percentage of diseased of 60% (150 of 250 subjects).

Under the assumption of maximum attrition of 20%, the sample size will be increased to 300 patients. The same sample size is sufficient to precisely estimate a logistic model of achievement of an MDA (probability of 0.4 at 6 months) with 10 predictors (rule of thumbs).

Based on the prestudy activities, 40 investigators will be involved, 15 from tertiary and 20–25 from secondary rheumatology centres. Enrolment will last 12 months at each participating centre; assuming four eligible patients per month for tertiary and one per month in secondary centres and a 40% enrolment rate, about 30 patients per month are expected.

Statistical analysis
Clinical data (including AEs and concomitant medications) will be entered into a validated data capture system provided by the Italian Society for Rheumatology. The data system will include password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete or inaccurate.

Descriptive data will be provided for all outcomes (table 2) according to data type; number of patients (N), mean, SD (for interval data), median 25% and 75% quartiles (for ordinal data). Frequency (absolute and relative) distributions will be provided for categorical data. Two-sided p values will be presented throughout. Data management and analysis will be performed using REDCap, R, Stata.

Primary endpoint analysis
Prediction of 6 months MDA will use multivariate adjusted logistic models. A baseline model will include all the clinical and treatment variables. US predictors will be added as covariates to the clinical variables, assuming an additive model. The derived ß coefficients were used to calculate prognostic indices, thereby creating weighted prediction models. Model performance will be evaluated by C-indices -area under the ROC curve (AUC), Net Reclassification Indices, integrated discrimination improvement and plotted ROC curves. A sensitivity analysis will also be performed excluding patients who experience AEs within 6 months (also based on their number).

Secondary endpoint analyses
The same approach followed for the primary endpoint will be followed to evaluate the additional value of US over clinical examination in detecting patients achieving secondary endpoints.

**DISCUSSION**
PsA is a chronic inflammatory disease which could have different clinical presentations (ie, peripheral arthritis, dactylitis, enthesitis or axial involvement) and different disease courses (eg, mild, intermittent or with high structural damage and disability). Considering the heterogeneous forms of PsA and the multiple available therapeutic targets (conventional, biological and synthetic targeted disease modifying antirheumatic drugs), we need predictors of response and remission in order to individualise treatment preventing high structural damage, disability and worsening of comorbidities. The UPSTREAM study aims to identify possible predictors of achieving MDA, remission in a wide cohort of PsA starting a new course of therapy for an active disease for peripheral arthritis and characterised by different types of treatment according to international guidelines and duration of the disease. To date, in PsA, clinical predictors of poorer outcome have not been clearly identified and nothing is still published on ultrasonographic predictors. Actually, the usefulness of US for diagnosis is established, while for prognosis and follow-up of chronic arthritis in clinical practice is still a matter of debate, despite the evidence of a higher sensitivity over clinical examination. The integration of US with clinical examination to stratify patients and to decide treatments in a T2T strategy represents an interesting challenge, and the UPSTREAM study aims to disentangle their possible combined role as predictors of treatment response. In PsA, identifying prognostic factors of MDA and remission will allow a better selection of patients with poorer outcome and possibly the improvement of therapeutic strategies.

**ETHICS AND DISSEMINATION**
Patient recruitment began in February 2017 at two centres (University Clinic AOU, Cagliari and University Hospital ‘Santa Maria della Misericordia’, Udine) and the trial will close to recruitment on March 2019. Results will be published in relevant scientific journals and be disseminated in international conferences. Fully anonymised data will be accessible from authors upon request.

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