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# THE REMISSION AND FLARE IN PSORIATIC ARTHRITIS (REFLAP) STUDY

**DEFINING CUT-OFF VALUES FOR WIDELY-USED COMPOSITE SCORES AND PATIENT-REPORTED OUTCOME MEASURES IN PSORIATIC ARTHRITIS, CORRESPONDING TO MINIMAL DISEASE ACTIVITY, PATIENT-REPORTED ACCEPTABLE STATE/REMISSION, AND FLARE ASSESSED BY THE PHYSICIAN AND THE PATIENT**

**A PROSPECTIVE 6-MONTH STUDY WITH A DOUBLE PERSPECTIVE**

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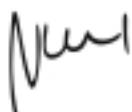
**Principal investigator** Laure GOSSEC, MD, PhD, France

**Contact:** Laure Gossec  
laure.gossec@aphp.fr  
Service de Rhumatologie, CHU Pitié Salpêtrière  
47-83 Boulevard de l'Hôpital, 75013 Paris, France  
+33 1 42 17 84 21

**Steering committee** Laura COATES, UK  
Maarten de WIT, Netherlands  
Ana-Maria ORBAI, USA  
Josef SMOLEN, Austria

**Promotor and sponsor** Groupe d'Etudes et de Recherche de l'appareil locomoteur (GERPAL), a non-for-profit hospital-based research association, president Pr Pierre Bourgeois, Hopital Pitié-Salpêtrière, 47-83 Bd Hopital, 75013 Paris France

**Principal investigator signature**



Laure Gossec, 21 April 2017

## Contents

Brief synopsis .....	3
Long Summary.....	5
Background.....	7
Objectives.....	10
Patients and methods .....	11
Study design .....	11
Patient research partner involvement.....	11
Patients.....	11
Data collection.....	13
Outcomes and planned analyses.....	19
Statistical analyses.....	20
Ethical and regulatory aspects .....	25
Practical aspects.....	27
Ccoinvestigators.....	27
Proposed calendar.....	29
Budget .....	30
Expected outcomes of the study.....	32
References.....	33

## **Brief synopsis**

### Objective

To define cutoffs of the most widely used composite scores and patient-reported outcomes (PROs), for levels corresponding to remission/low disease activity and for changes in levels corresponding to flares, in Psoriatic arthritis (PsA), from the patient and physician perspective.

### Methods

Design: the ReFlaP (Remission/Flare in PsA) study is a prospective, multicentric international, longitudinal, observational study planned in 2017-18 in 28 centers across Europe, North and South America and Asia. We plan to include 450 patients over 6 months (20-30 patients per centre). Each patient is seen twice: once at baseline and once at 1-6 months (follow-up visit, either for usual follow-up or because of a flare) in the context of usual care.

Patients: Consecutive adult patients with definite PsA (according to CIASSification of Psoriatic ARthritis (CASPAR) criteria and confirmation by a rheumatologist), and more than 2 years of disease duration.

Data collection: During each visit, physicians will collect: 66-68 joint counts, tender entheseal points and body surface area of psoriasis. This will allow calculation of: Arithmetic Mean of Desirability Functions modified, Disease Activity in PSoriatic Arthritis (DAPSA), clinical DAPSA, Minimal Disease Activity and Psoriatic ArthritiS Disease Activity Score. PROs will include will include Patient Global Assessment, Pain, Health Assessment Questionnaire for Disability Index, PSoriatic Arthritis Impact of Disease, Psoriatic Arthritis Quality of Life, 36-Item Short Form Health Survey (SF-36), PSoriatic Arthritis Impact of Disease, 12-Item Short Form Health Survey (SF-36), Patient Acceptable Symptom State (PASS), Minimal clinically important differences (MCID) and the recent Flare questionnaire. Assessment of disease activity status (i.e. remission or flare) will also be performed by both physician and patient using global questions.

### Planned analysis

From the health professional perspective, 'remission' will be defined as MDA and sensitivity analyses will use the other composite scores; flare will be defined as decision of treatment intensification and sensitivity analyses will be performed.

From the patient perspective, 'remission' will be defined as PASS and as sensitivity analysis, patient-perceived remission/low disease single questions, and for flares, the flare questionnaire, and as sensitivity analyses, flare according to the patient (single question) and the assessment of worsening based on the validated MCID question.

We will assess what physician and patient-defined states correspond to both on composite scores and on PROs, using baseline data for remission/low disease activity and changes in scores between the 2 visits for flares. Cutoff values for each outcome or change corresponding to clinically important differences will be calculated using ROC curves and 75<sup>th</sup> percentile analyses.

#### Planned outcomes

The expected outcomes are a better knowledge of remission/low disease activity and flare in PsA in accordance to the perspectives of patients and physicians. We will define cutoff values for most widely-used scores in PsA, allowing easier interpretation of study results and in the clinic, helping a better communication with patients in a treat-to-target approach.

## Long Summary

### Introduction

Psoriatic arthritis (PsA) is a heterogeneous chronic disease with a significant patient-perceived impact leading to pain, fatigue, impaired function and quality of life and psychological distress. Remission is the announced treatment target in PsA. Several definitions of remission have been proposed including definitions on composite scores such as the Disease Activity in Psoriatic Arthritis (DAPSA) and Minimal Disease Activity (MDA), however their translation into the patient's perspective is lacking. Flares are frequent in PsA and are important for patients but are not well-defined from the physician's perspective. Although some work is ongoing regarding remission and flare from the patient's perspective, currently no information allows to cross-tabulate and compare the patient and physician perspectives regarding remission and flare in PsA.

The objective is to define cutoffs of the most widely used composite scores and patient-reported outcomes (PROs), for levels corresponding to remission/low disease activity and for changes in levels corresponding to flares, in PsA, when remission/low disease activity and flare are defined from the patient and physician perspective.

### Methods

Design: the ReFlaP (Remission/Flare in PsA) study is a prospective, multicentric international, longitudinal, observational study. It will take place in 2017-18 in 28 centers across Europe, North and South America and Asia. We plan to include a total of 450 patients. The inclusion period will last 6 months; each center will include around 20 patients. Each patient is seen twice - once at baseline and once at 1-6 months (follow-up visit either for usual follow up or due to a flare) in the context of usual care.

Patients: Consecutive adult patients with definite PsA (according to CIASSification of Psoriatic ARthritis (CASPAR) criteria and confirmation by a rheumatologist), more than 2 years of disease duration, and will be included after signed informed consent.

Data collection: During each visit, physicians will collect data on the disease and on disease activity: 66 swollen joint counts, 68 tender joint counts, tender enthesal points (Leeds Enthesitis Index) and body surface area of psoriasis. This will allow calculation of most of the usual composite scores of PsA: Arithmetic Mean of Desirability Functions modified (AMDF modified), Disease Activity in Psoriatic Arthritis (DAPSA), clinical DAPSA (c-DAPSA), Minimal Disease Activity (MDA) and Psoriatic Arthritis Disease Activity Score (PASDAS). Well-validated patient-reported outcomes will be collected from patients: Patient Global Assessment (PGA), Pain, Health Assessment Quality (HAQ-DI), Psoriatic Arthritis Impact of Disease (PSAID) which includes a fatigue question, 12-Item Short Form Health Survey (SF-12), Patient Acceptable Symptom State (PASS) and the validated question for Minimal clinically

important differences (MCID) as well as a recent Flare questionnaire. Assessment of disease activity status (i.e. remission/low disease activity or flare) will be performed by both physician and patient using global questions.

### Planned analysis

To define cutoffs of the most widely used composite scores and PROs, for levels corresponding to remission/low disease activity and for changes in levels corresponding to flares, in PsA:

From the health professional perspective, the gold standard for 'remission' will be MDA and sensitivity analyses will use physician-perceived remission/low disease activity (single questions) and remission in composite scores (DAPSA, c-DAPSA, modified AMDF, PASDAS); for flare the gold standard will be decision of treatment intensification and sensitivity analyses will use: global assessment of flare and increase in category of disease activity in the composite scores.

From the perspective of the patient, the gold standard will be for 'remission', PASS and as sensitivity analysis, patient-perceived remission/low disease single questions yes/no, and for flares, the GRAPPA flare questionnaire, and as sensitivity analyses, flare according to the patient (single question) and the assessment of worsening in MCID.

We will assess what physician-defined remission/low disease activity/flare and patient-defined remission/low disease activity/flare correspond to both on composite 'physician' scores and on all the collected PRO scores. We will use data collected at baseline cross sectionally for remission/low disease activity and changes in scores between the 2 visits for flares.

Cutoff values for each outcome and for each change corresponding to clinically important differences in outcome will be calculated using ROC curves and 75<sup>th</sup> percentile analyses. Sensitivity analyses will explore cutoff values found according to patient demographic characteristics and country. We will compare attainment of remission or flare according to the different definitions, using kappa analyses. Rasch analyses will be used as necessary.

### Planned outcomes

The expected outcomes of this study are a better knowledge of remission/low disease activity and flare in PsA in accordance to the perspectives of patients and physicians. We will define cutoff values for most widely-used scores in PsA, allowing easier interpretation of study results and in the clinic, helping a better communication with patients.

Better knowledge of the important aspects of disease fluctuation and of patient relevant disease targets in PsA should enhance patient care and management in a treat-to-target approach.

## Background

Psoriatic arthritis (PsA) is a complex disease with inflammation that spans a wide spectrum to include peripheral joints, skin, entheses, spine, and other adjacent tissues. (Kleinert2007) PsA is an erosive and proliferative deforming arthritis usually accompanied by skin lesions as well as in some cases other manifestations.

Recent management recommendations state that remission is the treatment goal in PsA. (Gossec2016a, Coates2016a, Coates2016b) However, experts also recognize that remission is sometimes difficult to achieve and maintain and that, in some patients, some residual or mild disease activity may be acceptable. (Gossec2016a, Coates2016a) Thus, “near-remission” or “minimal/ low disease activity” could be an appropriate goal for treatment in some individual patients. (Kavanaugh2006, Gossec2016b)

**There are several definitions of remission and acceptable residual disease activity levels in PsA.** (Kavanaugh2006, Acosta2014) The Group for Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) suggested that remission in PsA should be characterized by “a complete absence of disease activity, with no signs or symptoms of active disease”. (Kavanaugh2006) In parallel, the European League Against Rheumatism (EULAR) defined remission in PsA as “the absence of clinical and laboratory evidence of significant inflammatory disease activity.” (Gossec2016a) Contrary to the situation in rheumatoid arthritis where a specific definition of remission has been proposed by a European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) consensus (Aletaha2010a, Bykerk2012), in PsA a specific and quantifiable definition of remission is lacking. However some approaches have been proposed recently based on physician consensus exercises and using composite disease activity scores. Remission and low disease activity definitions have been defined using the Disease Activity index for Psoriatic Arthritis (DAPSA) (Aletaha2016b) The DAPSA is composed of five untransformed, unweighted variables, including two patient-centered items (patient global assessment and pain on an 11-point numeric rating scale), one physician centered item (swollen joint count using 66 joints, 66-SJC), one item dependent on patient and physician (tender joint count using 68 joints, 68-TJC), and a laboratory variable (C Reactive Protein (CRP) in mg/dL). (Aletaha2016b) The DAPSA-based remission status (i.e., a score <4 points) is associated with no or minimal residual ultrasound signals in the joints. (Schoels2016) A clinical DAPSA score (c-DAPSA) is also available and is calculated using the same variables as DAPSA, without CRP. Other measures with validated definitions of remission include the Composite Psoriatic Disease Activity Index (CPDAI), the GRAPPA-developed PsA Disease Activity Score (PASDAS) and Arythmetic Mean of Desirability Functions (AMDF). (Mumtazz2011, Helliwell2014)

An alternative treatment target is Minimal Disease Activity (MDA). Minimal disease activity (MDA), agreed at the Outcome Measures in Rheumatology Clinical

Trials (OMERACT) 6 conference is defined as “that state of disease activity deemed a useful target of treatment by both the patient and the physician, given current treatment possibilities and limitations”. (Wells2005). Patients are classified as achieving MDA if they fulfill 5 of 7 outcome measures: tender joint count  $\leq 1$ ; swollen joint count  $\leq 1$ ; psoriasis activity and severity index  $\leq 1$  or body surface area  $\leq 3$ ; patient pain visual analog scale (VAS) score of  $\leq 15$ ; patient global disease activity VAS score of  $\leq 20$ ; Health Assessment Questionnaire (HAQ) score  $\leq 0.5$ ; and tender entheseal points  $\leq 1$ . (Coates2010b) The recently published Tight control in PsA (TICOPA) trial now provides evidence for treating to target using the MDA criteria. In this trial, patients with active PsA randomised to the tight control arm had a treatment escalation starting with conventional synthetic DMARDs up to biologics, if the pre-defined target of MDA was not reached: the group with tight control had more favorable clinical and patient reported outcomes. (Coates2013c)

**Remission from the patient perspective has not been defined.** The only data available are issued from qualitative studies and have not been further quantified or even graded for importance. These qualitative studies bring information on the patient experience of remission and other aspects of PsA (this work is underway as part of a GRAPPA/OMERACT initiative). PsA has a significant impact on patients' lives, as seen not only in qualitative studies but also through PRO (patient-reported outcome) assessments. The impact of PsA includes pain, fatigue, altered quality of life and impaired physical functioning as well as psychological impact. (Gossec2014, Strand2012). The wide-reaching impact of PsA has been recognized by OMERACT in the new updated Core Set for PsA (Orbai2016a). The Patient Acceptable Symptom State (PASS) is a well-validated single question which may approximate 'remission' for the patient since at least, it defines an acceptable state (Tubach2012, Heiberg2008).

PROs are an important component to assessing disease impact and therapy response in patients with PsA. (Strand 2016, Kirkham2015, Gniadecki2012) Many questionnaires and PROs are used in rheumatology. (OML) Some of these questionnaires assess a single aspect of disease impact: e.g., pain or patient global assessment (usually assessed using a numeric or visual rating scale) and physical functioning (usually assessed through the Health Assessment Questionnaire (HAQ) whereas others assess global impact of disease or quality of life. (Chandra2007, Pincus2007) These include generic questionnaires such as 36-Item Short Form Health Survey (SF-36), and disease specific questionnaires such as the EULAR-developed PsA Impact of Disease (PsAID) questionnaire or the PsA Quality of Life Scale (PsAQoL). (McKenna2004; SF36; Gossec2014c)

**Knowledge of meaningful cutoffs for both patients and physicians for PROs and PsA composite scores, corresponding to both physician-defined targets (such as MDA) and patient-defined acceptable states, will improve PsA disease activity targeting, management and long term patient outcomes. It is**

important to note that given the culture-dependent nature of PROs, an international study would be preferred to ensure generalizability of our findings. (Putrik2016)

**Another important concept in disease activity is flares.** Most studies describe flare as an absence of remission or absence of minimal disease activity though the notion of a change in status is important when defining flares.(Dougados2016) From the physician perspective, a change in therapy (intensification) could also be used as a surrogate marker of flare. (Alten2011); a flare can also be defined as a worsening of disease activity using composite scores.

**From the patient perspective, flares are a complex notion.** Recently, GRAPPA has developed a preliminary flare PRO. (Moverly2016a, Moverly2015b) in this work, 20 items were agreed on as important by patients and 23 by physicians to define a flare, 8 items were accepted by both with the notion of a recent change/increase in the number or combination of symptoms. The concept of flare covers articular, skin, emotional, participation and fatigue domains. These qualitative studies bring information on the patient perspective on what it means to be in flare. (Orbai2016, Moverley2016a, Moverley2015b)

To our knowledge, this flare questionnaire has not yet been validated and in particular it is unknown how flares assessed using this questionnaire relate to changes both in composite scores (i.e. mixing physician assessment and PROs) and in other PROs. **Quantification is needed to define cutoff values for change in usual composite scores and PROs, which would correspond to a flare** from the patient and physician perspectives in PsA.

**Overall**, there are no validated cut-off values of PROs and composite scores corresponding to different states of disease activity in PsA (namely, remission and flare).

**Such innovative data would be very useful in a ‘treat to target’ approach to allow mutual interpretation of patient and physician treatment objectives.**

## Objectives

- To define cutoffs of the most widely used composite scores (mixing physician assessment and PROs) and PROs, for disease activity levels corresponding to PsA remission/low disease activity and for change in level of disease activity corresponding to PsA flare, when remission/low disease activity and flare are defined from the patients' and physicians' perspectives.
- From the physicians' perspective, 'remission' will be defined by MDA and sensitivity analyses will use physician-perceived remission/low disease (single questions) and remission in composite scores (DAPSA, modified AMDF, PASDAS); flare will be defined as decision of treatment intensification and sensitivity analyses will use: global assessment of flare and increase in category of disease activity in the composite scores.
- From the patients' perspective, 'remission' will be defined as PASS attained and as sensitivity analysis, patient-perceived remission or low disease single questions yes/no, and flares will be defined using the GRAPPA flare questionnaire, and as sensitivity analyses, flare according to the patient (single question) and the assessment of worsening in MCID.

We will assess what 'physician-defined' remission/low disease/flare and patient-defined remission/low disease/flare correspond to both on composite 'physician' scores and on all the collected PRO scores. We will use cross-sectional data collected at baseline for remission and low disease activity; and changes in scores between the 2 visits for flares.

## **Patients and methods**

### **Study design**

This study is a pragmatic, prospective, multicentric and international, longitudinal observational study performed in usual care. It is planned to take place in 2017-18 in 5 participating centres in France, 15 other European tertiary rheumatology centers (Germany, Hungary, Ireland, Italy, Norway, Romania, Spain, Turkey and the UK), 4 centers in the USA, 2 centers in Canada, 1 in Brazil, and 2 in Asia (Singapore and Russia). The international aspect is important firstly to reflect the potential diversity of patient views across countries and cultures, and secondly to facilitate rapid patient inclusion.

### **Patient research partner involvement**

Rules proposed by EULAR and OMERACT are followed to facilitate patient involvement. (deWit2011, Cheung2014)

At the highest level: one patient partner (MdW) is part of the steering committee.

Three other patient research partners helped to finalize the study design and data collection including the remission/low disease and flare global questions, and will give feedback on the results of the study. The 3 patients are Laurence Carton (France), Heidi Bertheussen (Norway) and Jim Walker (Scotland).

A first teleconference and email exchanges with the 4 patient research partners with PsA was organized in March 2017 to elaborate the remission and flare gestalt questions; and a second teleconference with the same partners will allow to present, discuss and interpret findings from a patient perspective.

Of note, we will not perform qualitative work on remission and flares with patients to avoid duplicating ongoing efforts in this area. (Moverley2015b, Orbai unpublished)

## **Patients**

### **Patients' recruitment**

Over the 6 months recruitment period, all patients with definite PsA who satisfy the inclusion criteria, seen in outpatient visits in the participating centers by one of the investigators, will be asked to participate.

We expect a total of 700 patients will be contacted, to include 500 patients.

It is planned that in each center, 15-30 patients will be included. The first 15-30 consecutive patients will be selected in each center to reduce bias selection.

Each patient will be assessed, the first time, at the time of a scheduled visit in one of the participating centers according to local practice; and the second time, 1-6 months later, at the next consecutive assessment of his/her status according to usual practice. The choice of this second time point is important because as this is a 'non-interventional' study, there is no consensus about the period of follow-up between countries we are in a usual practice setting when leaving the choice open to the physician between 1 and 6 months.

Furthermore, the open timeframe will increase the probability to detect a flare since in many cases, patients will consult the physician in case of flare but this visit would be missed using a fixed time point.

We will encourage physicians to see patients if they are reporting a flare, as is recommended in a treat-to-target approach.

The follow-up for each patient will be of 1 to 6 months (last date allowed: 7 months).

#### Inclusion criteria

- Age > 18 years
- Definite PsA according to the CIASSification of Psoriatic ARthritis (CASPAR) criteria and diagnosis confirmed by a rheumatologist. (Taylor2006)
- Willingness to participate and signed informed consent.
- There are no inclusion criteria based on disease activity or treatment. Given the international study with countries with varied levels of health and of access to care and treatments, the study should include patients with a wide range of disease severity and activity at baseline.
- Patients with more than 2 years of disease duration will be included in the study for more homogeneity.

Patient will be included consecutively. A registry will be kept locally to note the age and gender of patients who have been proposed the study but refused to participate.

#### Exclusion criteria

- No definite PsA or less than 2 years of disease duration

- Patients who don't speak or read the local language or are not comfortable filling in a paper CRF in the local language.

## **Data collection**

Each patient is assessed twice, at both assessments the same data are collected except for data which do not change such as demographic data (**Table 1**).

To avoid circularity, physician questionnaires will be filled after the patient questionnaire (which is done alone by the patient) and physicians will fill it without looking at the patient questionnaire (however they can collect PROs according to their usual practice).

### **Physician CRF (Table 1)**

Characteristics of the patients will be collected by the health professionals, physicians or research nurses in the physician CRF: sex, age, year of PsA diagnosis, work status, treatments (including biological therapy), CASPAR criteria. (Taylor2006) The predominant type of PsA (peripheral, axial or enthesseal) will be collected and current types of involvement will be collected.

A validated comorbidity index will be collected. (Groll2005)

### Elaboration of the physician questions for remission/ flare

Global questions for remission/low disease and flare were elaborated for the purpose of this study since none exist. There global questions were developed by the steering committee.

### Physician data regarding disease activity including physical examination

Physicians will fill in all the information necessary to calculate the following composite scores: DAPSA remission, DAPSA Low Disease Activity (using both DAPSA and c-DAPSA), PASDAS remission, AMDF modified remission, MDA and its several versions including MDA where both joint measures are mandated, MDA where the skin measure is mandated, MDA where these three are mandated and Very Low Disease Activity (VLDA) corresponding to all MDA criteria fulfilled. (Schoels 2015, Smolen2015, Mumtaz2011, Helliwell2014, Coates2010, Coates2016a, Coates2016d)

This includes a physical assessment with 66 swollen joint counts, 68 tender joint counts, tender enthesal points (Leeds Enthesitis Index), body surface area of psoriasis and physician global assessment. Weight and height will also be collected.

Physicians will also answer general questions on their gestalt on the disease status (remission/low disease activity or flare, please see above). To better understand the reasoning of the physician, specific questions related to the perceived cause of current symptom levels will also be asked: causality of patient symptoms between disease activity, sequels of disease or comorbidities. (as was the case in a recently-completed study in spondyloarthritis, Dougados 2017)

Here we are using a modified AMDF with no PASI replaced with skin global assessment and body surface area, to facilitate feasibility of data collection in rheumatology clinics. Furthermore the PsA Quality of Life score which is part of AMDF will not be collected: thus this is a modified AMDF. (McKenna2004, Mease2016)

We are aware we will not be collecting the data needed to calculate the Composite Psoriatic Disease Activity Index (CPDAI) for feasibility reasons. However a modified CPDAI may be calculated based on available data.

We will avoid circularity by not calculating the composite scores in the CRF.

### Blood test results

No specific blood tests will be performed for this study.

The last available results (<4 weeks) for C Reactive Protein will be collected in the CRF and when answering the CASPAR criteria questions, the physician will be asked for Rheumatoid Factor test results (in the patient's lifetime).

### Radiographic assessment

The last available X-Rays of hands and feet will be assessed locally by the health professional to answer the CASPAR question on the presence or not of specific radiographic changes.

### Treatment changes

Physicians will collect patient treatments for PsA and will answer if the treatment is changed or not and in which way (i.e., intensification, yes/no) at each visit.

## Patient CRF (Table 1)

### General questions

Question regarding demographic data and smoking status as well as current levels of physical exercise will be asked.

### Elaboration of the patient questions for remission/ flare

For these questions, flare and remission/low disease activity questions were developed for the purpose of this study. Patients will answer a specific targeted question on their assessment of remission yes/no and low disease activity yes/no. These unique and binary questions were refined with our 4 patient research partners because none exist in PsA. For flares also, we developed a binary question with the patient partners: using as basis the GRAPPA Flare pivotal question as well as previous work in the field of rheumatoid arthritis (Moverley 2016, Alten2011, Bykerk2016)

The questions were elaborated in a teleconference in March 2017 with the 4 patient research partners with PsA. The goal was to elaborate a global question for remission, and for low disease activity, and a global question for flare. A translation of the flare/ remission/low disease activity questions will be performed by 2 persons.

### Patient generated data regarding disease activity

PROs will be collected for PsA patients, at baseline and 1-6 months later at the second visit. Given difficulties with international authorizations for online data collection, the data will be collected anonymously in paper format.

#### *Remission assessment*

The Patient Acceptable Symptom State (PASS) will be assessed: this corresponds to the clinically relevant cut-off from the patient's perspective allowing classification of patients as being in « an acceptable state » or not with one question ("If you were to remain for the rest of your life as you were during the last 48 hours, would this be acceptable or unacceptable for you?"). (Tubach2012, Wariaghli2012) The PASS will be collected at baseline and at the second visit. (Heiberg2008, Tubach2012)

Patients will also answer a specific targeted question on their assessment of remission yes/no and of low disease activity (please see above).

#### *Flare*

Only flares at the time of assessment are targeted (and not recall of previous flares).

To assess flares from the patient perspective, the preliminary GRAPPA flare instrument will be evaluated: 1.A recent change in joint pain.2.A recent change in location of symptoms (i.e., sudden increase in pain or swelling in hands/feet).3.A recent change in the number of tender and/or sore joints. 4. A recent change in the

number of aching joints. 5. The presence or degree of pressure-sensitive joints. 6. A recent change/increase in the number of swollen joints. 7. A recent change/increase in night pain. 8. A recent change/increase in the number or combination of symptoms (**Table 1**). (Moverly2016a)

Patient will also answer a specific targeted question on their assessment of flare yes/no (see above).

The Minimum Clinically Important Difference (MCID) question gives information on change in disease status. The question is: "How would you describe your overall status since your last visit: much better, better, the same, worse, much worse?" Here, worse or much worse will be used to define a flare. (Curtis2015)

### *Composite PROs*

The PsAID is a questionnaire that can be used to calculate a score reflecting the impact of psoriatic arthritis (PsA) from the patients' perspective. (Gossec2014e)

The 12-Item Short Form Health Survey (SF12) is a multi-purpose, generic health survey. (SF36 online) It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. A physical summary score (physical composite score: PCS) and a mental summary (mental composite score: MCS) are calculated according to an established algorithm. PCS includes physical function, physical role, bodily pain and general health and MCS includes mental health, emotional role, social function and vitality. The SF-12 is copyrighted. It can be used instead of SF-36 in composite scores, as recently proposed.

### *Unidimensional PROs*

Patient Global Assessment (PGA) (on a 0–10 scale) asks the patient to give an overall assessment of how the arthritis is doing, thereby integrating a number of dimensions related to disease activity or to other aspects. The wording of questions and anchors are usually as follows: for the PGA, 'Considering all of the ways your arthritis affects you, mark "X" on the scale for how well you are doing' ('very well' to 'very poor').

Patient global for skin and for joints will also be evaluated on a numeric scale from 0 to 10 since part of the AMDF. (Helliwell2013) This will also give some indication on patient-perceived skin involvement.

Pain will be evaluated on a numeric scale from 0 to 10.

Fatigue will be analysed also (it is included in the PsAID).

The HAQ-Disability index is a disability questionnaire which includes 8 domains scored on a 0-3 scale (0 = without any difficulty, 1 = with some difficulty, 2 = with much difficulty, 3 = unable to do). (Pincus2007)

The validated single questions to define Minimal Clinically Important Difference (MCID) and PASS will be assessed as explained above.

## **CRF translations**

The physician CRF does not need to be translated. In the patient CRF, existing validated translations of the tools integrated in the CRF will be used. The rest of the CRF (i.e., demographic data etc) will only have a simple translation (by one person).

For the global remission and flare questions as well as for the Leeds Flare questionnaire, we need to perform translations since some of these questions were developed for this study (remission/flare questions) and the Leeds Flare questionnaire is not translated.

We will follow a simplified but validated translation and cross cultural adaptation process (Guillemin1993, Beaton2000).

Step 1: Two persons (at least 1 rheumatologist, at least one bilingual person, and wherever possible also a patient research partner) translate independently the English version into the target language.

Step 2 : consensus between the translators leads to a final version. Please keep in mind that the final wording needs to be understood by lay people including low-education people ("the aim is for a 9-yr old child to understand the wording").

Step 3: Backward translation of the new-language version into English is performed by an independent bilingual native English speaker, blinded to the English original version.

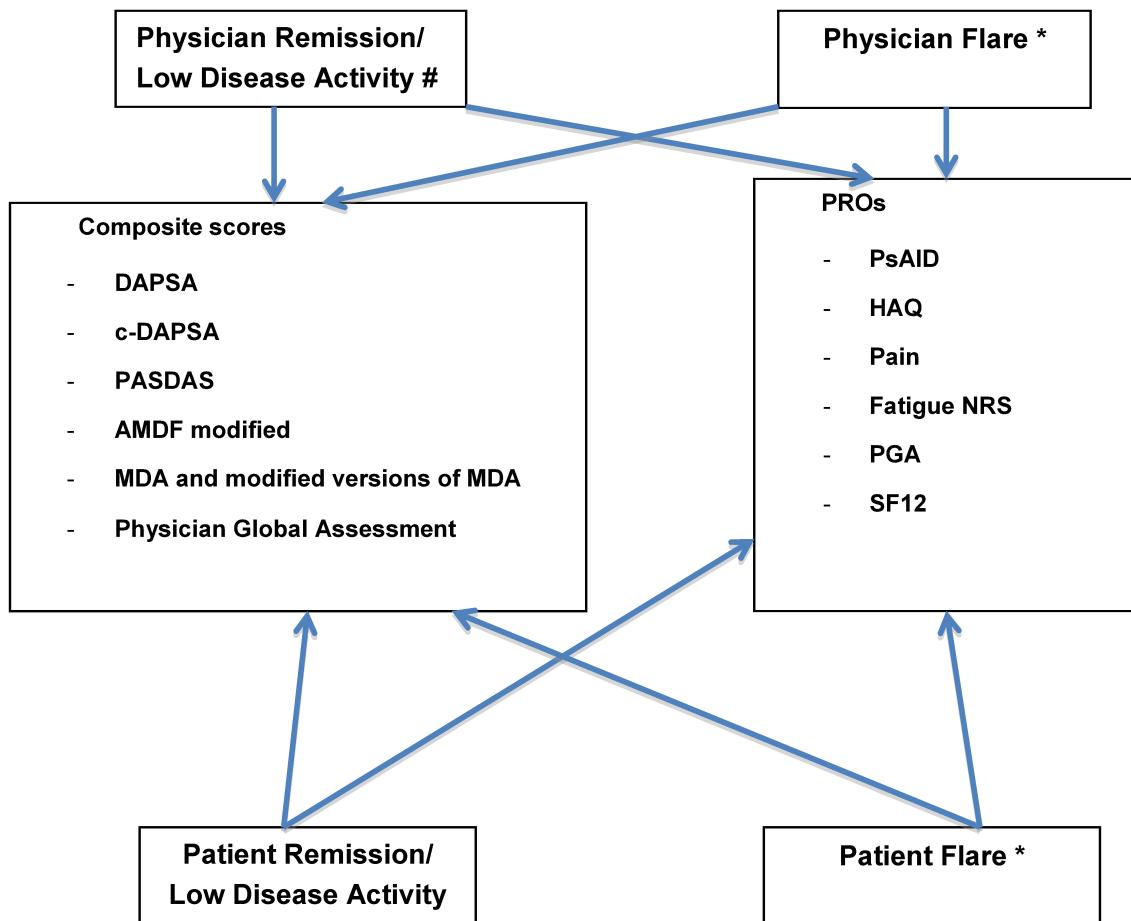
Step 4: consensus meeting between the translators to check the meaning has not been changed or lost. The group will compare the initial version and the back-translation and will discuss the phrasing of the target-language version, and by consensus will produce a final version. The committee has to ensure that the translation is fully comprehensive and to verify cross-cultural equivalence of the source and final versions. Please keep in mind again at this phase that the final wording needs to be understood by lay people including low-education people.

**Table 1: data collection**

Type of data	Collected data	Baseline	1-6 months
Patient CRF	Identifying initials and patient number	X	X
	Gender	X	
	Smoking status, height and weight	X	
	Exercise levels	X	
	Patient Pain Visual Analogue Score	X	X
	Patient VAS for skin	X	X
	Patient VAS for joints	X	X
	Patient's Global Assessment of Disease Activity	X	X
	Health Assessment Questionnaire	X	X
	SF-12	X	X
	PsAID-12	X	X
	Disease status: remission yes/no, low disease activity yes/no, flare yes/no, and number of recent flares	X	X
	MCID	X	X
	GRAPPA flare instrument	X	X
	PASS	X	X
Physician CRF	Year of birth of the patient	X	
	CASPAR criteria (individual criteria)	X	
	Confirmation of PsA by the physician	X	
	Year of PsA diagnosis	X	
	Treatments	X	X
	Level of studies	X	
	Physician Global Assessment	X	X
	Predominant type of PsA: axial, peripheral, enthesitic	X	
	Tender joint count (68)	X	X
	Swollen joint count (66) and deformed joints	X	X
	Body surface area of Psoriasis (%)	X	X
	Tender enthesal points (Leeds Enthesitis Index)	X	X
	CRP	X	X
	Comorbidity index (Groll2005)	X	
	Disease status: remission yes/no, low disease activity yes/no, flare yes/no, qualitative questions regarding cause of symptoms	X	X
	Treatment intensification (yes/no)	X	X

## Outcomes and planned analyses

Of note, as the concepts of remission and flare are not well defined and there is no gold standard, we have to 'go around' the concept using several partial gold standards. This explains the multiple analyses (**Figure**)..



# Assessment of levels of scores

\* Assessment of change in scores between the 2 visits

We plan to define cutoffs of the most widely used composite scores and PROs, for levels corresponding to remission/low disease activity and for changes in levels corresponding to flares, in PsA, when remission/low disease activity and flare are defined from the patient and physician perspective.

**To this end we will 'define' remission and flare as follows:**

**From the physicians' perspective**

-the main definition for 'remission' used here will be MDA

-and sensitivity analyses will use the treating physician-perceived remission or low disease (single questions), other definitions of MDA as recently proposed, and remission in composite scores (cutoffs have been defined for DAPSA, modified AMDF, PASDAS);

- for flare the gold standard will be decision of treatment intensification

-and sensitivity analyses will use: global assessment of flare and increase in category of disease activity in the composite scores.

### **From the patients' perspective**

-the main definition will be for 'remission', PASS

-and as sensitivity analysis, patient-perceived remission or low disease single questions yes/no,

-and for flares, the GRAPPA flare questionnaire,

-and as sensitivity analyses, flare according to the patient (single question) and the assessment of worsening in MCID.

### **Obtaining cutoffs**

We will assess what physician-defined remission/low disease activity/flare and patient-defined remission/low disease activity/flare correspond to both on composite 'physician' scores and on all the collected PRO scores (**Figure and Table 2**). We will use data collected at baseline cross sectionally for remission and low disease activity and changes in scores between the 2 visits for flares.

We will use data collected at baseline and at 1-6 months since flare is usually referred to as a change in disease status and indeed we are planning to define cutoff values for change in each outcome, corresponding to a flare.(Gossec2016)

Although we are aware the cutoff values obtained may differ between physicians and patients, we are not planning a reconciliation exercise.

### **Statistical analyses**

#### *Sample size*

The sample size is calculated to be able to determine the cutoff value of PsAID corresponding to remission or flare with a certain precision.

With a standard deviation of 2.30 as observed in the PsAID development study on 107 and 475 patients, with a confidence level of 0.95 and a precision of 0.05, it is necessary to analyse 82 patients in 'remission' (whatever the remission definition) or in flare. Since we expect around 20% of patients to be in remission in this usual practice cohort (given percentages of MDA are around 40-50% in randomised clinical trials of biological), and around 20% of patients to be in flare, we need to analyse a total of 410 patients for remission, thus we need to include 450 patients (taking into account uninterpretable CRFs due to missing data). (SAMPLE, Möttönen1999). For flares we are aware the sample size will be slightly smaller (taking into account patients having had a treatment intensification will not be assessed the second time), however for this exploratory analysis the sample size is considered sufficient for flares.

### *Planned analyses*

Population: Analyses will be performed on all included patients with data available regarding the remission and flare status questions.

For remission, all included patients with data available regarding remission will be assessed. The primary analysis is on baseline data. The data from the second visit will be seen as confirmatory and will be analysed as longitudinal data accounting for multiple visits.

For flare, only patients with both visits completed will be used. Change in outcomes between the 2 visits will be assessed.

Similarly to what has been done in axial spondyloarthritis (and differently to what has been done in rheumatoid arthritis), it is decided that flare will be defined as a change in status between the 2 time points, i.e., a flare is an absolute or relative change between 2 values: the observed value of the outcome at the time of the flare, minus the referral value (previous status before the flare). (Gossec2016, Bykerk2016)

The patient's initial status (referral value of the outcomes at the first visit) may vary from no symptoms to moderate/high disease activity but we will analyse separately patients with very high initial values, since it is considered that definitions of flares are only relevant for patients initially not in very high disease activity.

### Planned analyses:

Cutoff values for each outcome and for each change in outcome will be calculated using ROC curves and 75th percentile analyses (**Table 2 and 3**). For ROC curves, different cutoffs will be calculated, both using Youden's statistic (maximizing both sensitivity and specificity) but also using a fixed specificity number (80%) since specificity is more important than sensitivity in this case (to avoid overdiagnosing

flares). The 75<sup>th</sup> percentile technique is a classical technique which finds the value above which, 75% of patients reporting an outcome or a change in outcome, are placed. Rasch analysis will be used as appropriate. (Tubach2005, Machado2016) These techniques are widely used to determine cutoff values for continuous scores and are recommended by COSMIN (Mokkink2016/ website.cosmin)

Sensitivity analyses will explore cutoff values found according to patient demographic characteristics and country.

We will compare attainment of remission/low disease activity or flare according to the different definitions, using kappa analyses and logistic regression analyses will explore characteristics of patients who are in 'discordance' or not for flare/remission with the physician-defined definition, and physicians who are in 'discordance' with patients as well.

Missing data: All data will be analysed. To minimize missing data, the order of questions will also be studied to motivate respondents to finish the entire questionnaire.

**Table 2.** Planned analyses: defining cutoff values according to different definitions of remission/low disease activity (LDA)

Gold standards are below	MDA	Modified versions of MDA	Physician Gobal Assessment	DAPSA/c-DAPSA	PASDAS	Modified AMDF	PsAID	HAQ	Pain	Fatigue	PGA	SF12
MDA												
modified versions MDA												
<i>Physician remission/LDA single questions</i>												
Physician Global Assessment<4/10												
Composite score DAPSA												
Composite score PASDAS												
PASS												
Patient remission/LDA single questions												

**Table 3.** Planned analyses: defining cutoff values for change of outcomes according to different definitions of flare

Gold standards are below	MDA	Physician global ass.	DAPSA/c-DAPSA	PASDAS	Modified AMDF	GRAPPA flare questionnaire	PsAID	HAQ	Pain	Fatigue	PGA	SF12
Treatment intensification												
Physician flare single question												
Composite score DAPSA change in category												
Composite score PASDAS change in category												
GRAPPA flare questionnaire												
Patient flare single question												
Worsening MCID												

## **Ethical and regulatory aspects**

The promoter and sponsor of this observational study is a non-for-profit hospital-based research association, the Groupe d'Etudes et de Recherche de l'appareil locomoteur (GERPAL), president Pr Pierre Bourgeois, Hopital Pitié-Salpêtrière, 47-83 Bd Hopital, 75013 Paris : Association Loi 1901 – SIRET number : 404 828 527 00014 - Code APE : 731 Z, telephone +33142177801.

The Principal Investigator is Laure Gossec MD PhD.

### Participation request

Around 600 consecutive patients with PsA will be contacted during outpatient visits and will be asked to participate to the study. They will be given full information on the study.

Patients who are willing to participate are asked for a signed informed consent.

All patients will receive at inclusion full information. On this document will be clearly indicated how to un-register from the trial. The participants will have the opportunity to leave the study at any time. According to the participant's will data previously recorded could be kept in the database for analysis or deleted. The participants can have access to their data and correct them if requested.

### Personal information management

The local investigators will keep a confidential correspondence list of patient identifiers and of patient numbers.

The centralized information will consist entirely of de-identified data.

### Regulations and Review Boards

The study will be conducted in accordance with the protocol, ICH Good Clinical Practice, ethical principles that have their origin in the Declaration of Helsinki and all applicable local regulations.

Independent Ethics Committee or Institutional Review Board approval of the protocol will be obtained prior to commencing the study at each site, through the principal investigator and designated investigators. The details will be determined in each clinical setting that participates in this study.

This study is considered as 'non-interventional'. It will be presented to approval of an ethical committee for France. Ethical committees in each country will be

solicited by the principal investigators. A notice to the CCTIR and a request for authorization to the CNIL will be submitted for France and necessary authorisations will be obtained prior to the study in each participating country.

An Institutional Review Board approved, study-specific informed consent will be reviewed, signed and dated by the subject (and the investigator) prior to the performance of any study-related procedures.

### Protocol registration

The protocol will be registered in clinicaltrials.gov.

### Data Quality Assurance

#### *Data treatment.*

Patients will be identified by a local number at each investigator site, which will have a 3-letter code for a site and a number for each patient. Each site will keep a confidential subject identification code list, so that if there are missing data this information will be available locally to clarify the information.

All results will be forwarded anonymously (without identifying number, see above) to the data center in Paris, France to be entered (double data entry) into a pooled database. Data will be stored and analysed anonymously.

#### *Quality control*

There are several levels for quality control.

A. Locally for each CRF.

Last question of the CRF for the investigator: “Have you checked that the patient has filled in all the questions of his/her CRF, and have you filled in all the questions of your questionnaire?”

B. Central quality control.

CRFs will be sent by the national PI to the statistical center, Paris, every 10 CRFs, to be checked centrally for quality control.

## Practical aspects

### Coinvestigators

This project is a collaborative effort of 23 centres from 16 countries, which contribute medical data collected on their patients for central data analysis.

In order to analyse the data and in the interest of all participants, the study coordinators (i.e. each investigator in the list below) are responsible for correct data procurement, delivery of analysis results to the participants and development of agreed publication strategies.

**Table 4** shows the list of investigators. Each center will include between 15 and 30 patients.

Investigator engagement is formalized by an investigator contract and includes:

A- Translation of the CRF as needed, following the procedures for correct translation as outlined in the Study Protocol.

B- Obtainment of all necessary authorizations to perform the study in accordance with all applicable regulations.

C- Inclusion of consecutive patients with PsA who fulfill the inclusion criteria and who accept to participate.

The objective is to include 15-30 patients per centre. This contract will not influence your management procedures or therapy choices for the patient (observational study).

D- Upkeep of a patient log with patient identification (to be kept locally)

E- Collection at baseline of the CRF data from patient and physician on the paper CRF, and collection again of data at the next consecutive visit (planned according to usual care).

F- Transmission of the CRFs without any identifying information (anonymised data) to the principal investigator for central data entry in France.

Coauthorship in the final scientific publication(s) will be proposed to investigators who have contributed at least 15 full patients and who satisfy international authorship criteria. Of note, only one investigator per centre can be coauthor.

**Table 4. Coinvestigators**

Country	Identity	Centre	Role
Austria	Smolen Josef S.	Medical University of Vienna, Vienna, Austria	Co-investigator and steering
Brazil	Palominos Penelope	Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil	Co-investigator
Canada	Aydin Sibel	Ottawa University School of Medicine, Ottawa, Canada	Co-investigator
Canada	Eder Lihi	University of Toronto, Toronto, Canada	Co-investigator
Estonia	Talli Sandra	Tallinn Central Hospital, Tallinn, Estonia	Co-investigator
France	Dernis Emmanuelle	Le Mans Central Hospital, Le Mans, France	Co-investigator
France	Gossec Laure	CHU Pitié Salpêtrière, Paris, France	Co-investigator and steering
France	Richette Pascal	Lariboisiere Hospital, Paris France	Co-investigator
France	Ruyssen-Witrand Adeline	Pierre-Paul Riquet Hospital, Toulouse, France	Co-investigator
France	Soubrier Martin	Gabriel Montpied Hospital, Clermont Ferrand, France	Co-investigator
Germany	Kiltz Uta	Herne and Ruhr-Universität Bochum, Herne, Germany	Co-investigator
Ireland	Veale Douglas	St Vincent's University Hospital, Dublin, Ireland	Co-investigator
Italy	Scrivo Rossana	Sapienza Università di Roma, Rome, Italy	Co-investigator
Italy	Lubrano Ennio	Universita degli Studi del Molise, Campobasso, Italy	Co-investigator
Netherlands	Vis Marijn	Erasmus University Rotterdam,	Co-investigator

		Netherlands	
Romania	Balasescu Andra	Sf Maria Hospital, University of Medicine and Pharmacy Carol Davila, Bucharest, Romania	Co-investigator
Russia	Gaydukova Inna	Saratov State Medical University, Saratovskaya oblast', Saratov, Russia	Co-investigator
Singapore	Leung Katy	Singapore General Hospital, Singapore	Co-investigator
Spain	Canete Juan D	Hospital Clínic and IDIBAPS, Barcelona, Spain	Co-investigator
Turkey	Kalyoncu Umut	Hacettepe University, Ankara, Turkey	Co-investigator
UK	Coates Laura	University of Oxford Medical School, Oxford, UK	Co-investigator and steering
USA	Orbai Ana-Maria	Johns Hopkins University, Baltimore, USA	Co-investigator
USA	Husni Elaine	Cleveland Clinic Main Campus, Cleveland, USA	Co-investigator

### Proposed calendar

- 1<sup>st</sup> Jan 2017- 30<sup>th</sup> June 2017: Study protocol and CRF finalisation, translations and regulatory authorisations
- 1<sup>st</sup> May 2017 to 30<sup>th</sup> December 2017: Patient inclusion and data collection (baseline).
- 1<sup>st</sup> June 2017 to 31<sup>th</sup> July 2018: Second assessment / second patient visit
- September 2018: Statistical analysis.
- September-December 2018: Manuscript(s) preparation.

The study initiation will necessitate a 2-hour investigator webconference, then follow-up investigator meetings will be performed during international congresses and by regular web conferences.

The project progress will be monitored by two-month-reports prepared by the investigators and forwarded to the study coordinators.

The results will be presented primarily at international meetings but also at national meetings by the individual investigators. The final manuscript(s) will be submitted to international rheumatology journals. All national investigators who have included at least 15 patients (one representative per center) and the steering committee will be coauthors.

## **Budget**

The total budget for this study is calculated at 160 000 euros. The detailed budget is below in Table 3.

This budget includes central funds for study coordination and analyses, and local funds for each investigator's center for translations, ethical submissions and patient inclusions. It is expected 450 baseline visits and 400 second visits.

Financial support is sought from Pfizer through an unrestricted research grants (investigator initiative research grant) and acceptance is obtained on April 20,2017.

### **Financial compensation for investigators**

The compensation is planned as follows:

- CRF translation (300 euros per language)
- Ethical consent obtainment (400 euros per country, to be paid to the centre which performed the process in case of several centres per country)
- Remuneration for each patient included (100 euros per first visit and 75 per second patient visit)

Thus for a centre including 20 patients, the total sum payable will be 4200 euros.

Payment shall be made within 30 days of receipt and approval of invoices. The investigator is responsible for the payment of any applicable taxes associated with the receipt of the compensation.

**Table 3 Budget**

Expenses	Total Budget (Euros)	Budget for first year (2017)	Budget for second year (2018)
Project management	10 000	5 000	5 000
Study organisation and follow up	16 000	8 000	8 000
Patient research partner contribution	4 000	2 000	2 000
Steering committee honoraria (1000 per person)	5 000	2 500	2 500
CRF translation (300 per language, 10 languages)	3 000	3 000	0
Ethical submission (400 per country, 15 countries)	6 000	6 000	0
CRF printing and mailing	3 000	2 000	1 000
Remuneration for each patient included (100 per first visit and 75 per second patient visit)	75 000	45 000	30 000
Double data entry	6 000	3 000	3 000
Statistical analyses	15 000	2 000	13 000
Copyrighted questionnaire fees (SF-12)	2 000	1 000	1 000
Accounts and taxes (10%)	15 000	8 700	6 300
<b>TOTAL</b>	<b>160 000</b>	<b>88 200</b>	<b>71 800</b>

## **Expected outcomes of the study**

The expected outcomes of this study are a better knowledge of remission and flare in PsA with a cross-tabulation of the perspectives of patients and physicians. The quantitative data will allow to calculate cutoff values for scores used in PsA which will facilitate shared decision making in a 'treat to target' approach and the interpretation of future studies and clinical trials in the field of PsA.

The international nature of the study will enhance external validity of the results given the subjective nature of patient assessments of flare and remission (Putrik2016)

Better knowledge of the important aspects of disease fluctuation and of patient relevant disease targets in PsA should enhance patient care and management.

The present study is in line with recent EULAR recommendations for future research in PsA, i.e., the research agenda developed by the EULAR management taskforce. (Gossec2016a)

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