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Running Head: Composites for PsA Trials

Composite Measures for Clinical Trials in Psoriatic Arthritis: Testing Pain and Fatigue Modifications in a U.K. Multicentre Study

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Ethical Approval: Ethical Approval for this study was given by the North East York Research Ethics Committee Ref: 17/NE/0084. All patients signed written consent in accordance with the declaration of Helsinki.

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"As part of the supplement series GRAPPA 2020, this report was reviewed internally and approved by the Guest Editors for integrity, accuracy, and consistency with scientific and ethical standards."

ABBREVIATIONS

CPDAI, Composite Psoriatic Arthritis Disease Activity Index; **DAS**, Disease Activity Score; **DAPSA**, Disease Activity in Psoriatic Arthritis; **GRACE**, GRAPPA Composite Exercise; HAQ, Health Assessment Questionnaire; LDI, Leeds Dacylitis Index; **LEI**, Leeds Enthesitis Index; **MDA**, Minimal Disease Activity; **PASDAS**, Psoriatic Arthritis Disease Activity Score; **PASI**, Psoriasis Areas Severity Index; **PROMS**, Patient Reported Outcome MeasureS; **PsA**, Psoriatic Arthritis; **SRM**, Standardized Response Mean; **VAS**, Visual Analogue Scale

Word Count: 2678

ABSTRACT

Objective. To test the addition of pain and fatigue to the CPDAI and GRACE composite measures of Psoriatic Arthritis (PsA).

Methods. Clinical and patient reported outcome measures were assessed in patients with PsA at three consecutive follow up visits over 6 months in a U.K. multicentre observational study. A pain VAS and FACIT-fatigue were added as modifications to the CPDAI and GRACE composite measures. Original and modified versions were tested against the PASDAS and DAPSA. Discrimination between disease states and responsiveness were tested with the t-score, SRM and effect size. Data were presented to members at the 2020 annual meeting and voted on the GRAPPA recommended composite and treatment targets for clinical trials.

Results. 139 patients were recruited with a mean psoriatic arthritis duration of 6.1 years (0 – 41 y). The SRM for the GRACE/mGRACE 0.67/ 0.64 and CPDAI/ mCPDAI 0.54/ 0.46, respectively. The t-scores for the GRACE/mGRACE was unchanged at 7.8/7.8 and CPDAI/ mCPDAI was 6.8/7.0, respectively. The PASDAS demonstrated the best responsiveness (SRM=0.84) and discrimination (t-score 8.3). Most (82%) members agreed the composites should not be modified and 77% voted for the PASDAS as the GRAPPA recommended composite for clinical trials and 90% the MDA as the target.

Conclusion. Modifying the CPDAI and GRACE with the addition of pain and fatigue does not enhance responsiveness nor their ability to detect disease status in terms of requiring treatment escalation. GRAPPA members voted for the PASDAS as the composite measure in clinical trials and MDA as the target.

INTRODUCTION

Psoriatic arthritis (PsA) is an inflammatory arthritis occurring in up to 30% of patients with psoriasis (1). Prospective studies of PsA have demonstrated progression of clinical joint destruction, deteriorating functional status and a negative impact quality of life and ability to work (2,3). Psoriatic arthritis is a heterogeneous disease that can manifest in several ways including arthritis, spondylitis, enthesitis, dactylitis, iritis, as well as skin and nail disease. Historically the primary outcome measure in PsA trials have been measures focusing solely on the articular manifestations of disease such as the Disease Activity Score 28 (DAS 28) or American College of Rheumatology 20% improvement criteria (ACR20) (4,5). There has been concern that applying a rheumatic arthritis paradigm of assessment by focusing solely on articular disease may underestimate the burden of disease and response to treatment in PsA.

Continuous composite measures of disease activity that include more domains of disease have been developed (6). Candidate continuous composite measures outcomes measures include: the Psoriatic Arthritis Disease Activity Score (PASDAS) (7), Composite Psoriatic Arthritis Disease Activity Index (CPDAI) (8), GRAPPA Composite Exercise (GRACE) (7) and Disease Activity in Psoriatic Arthritis (DAPSA) (8). In addition to these continuous measures the Minimal Disease Activity (MDA) is proposed as a treatment target representing low disease activity (9). The MDA is a response criterion, a state representing low disease activity that is either achieved or not. The MDA was used as the target in the Tight Control of Psoriatic Arthritis (TICOPA) trial (10).

Continuous composite measures were the subject of a workshop at the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) annual meeting in 2019 (11). Members reviewed the existing continuous composite measures and outcomes important to patients (12,13) and discussed each composite in breakout groups and reported the respective benefits, limitations and barriers to their wider adoption (11). Barriers included the poor representation of high priority outcomes to patients, such as pain and fatigue and members voted to test modifications (14). We report the testing of modified versions of the CPDAI/GRACE to the original versions (PASDAS and DAPSA), followed by discussion and voting from the composites session at the GRAPPA 2020 annual meeting.

MATERIALS AND METHODS

ASSESS study design

Patients with PsA according to the CASPAR criteria (15) were sequentially recruited from the Royal National Hospital for Rheumatic Diseases (RNHRD), Bath and six other centres across the United Kingdom (UK). Participants received routine care from their rheumatologists based on current best practice. Study visits were scheduled at baseline, 3 months and 6 months. A comprehensive clinical assessment was conducted at each clinical visit including patient reported outcome measures (PROMS), as shown in Supplementary Table 1 and clinical assessments [tender and swollen joint count, Leeds enthesitis and dactylitis count, Body Surface Area (BSA) of psoriasis (%), Psoriasis Areas and Severity Index (PASI)], physician global score (0-5) and C-reactive protein.

Based upon the clinical assessment at each visit, the treating physician determined whether treatment change was required and if a treatment change was actually implemented. The decision to change treatment was used as a proxy for active disease regardless of whether the patient actually changed treatment (medication increase or addition of new medication-specified in Supplementary Table 2). If treatments were changed because of an adverse event, cases were excluded from the "changed medication" group. If no treatment change was required, this was regarded as surrogate for stable disease. If no treatment change was required participants were asked to return 1 week later to repeat the assessments, thereby allowing assessment of test re-test reliability. Patients were therefore classified into 2 groups: those with active disease (requiring a change in treatment) and patients with low disease activity /remission, not requiring treatment change).

Composite measures and modifications

The Composite Psoriatic Arthritis Disease Activity Index (CPDAI) measures disease activity in five domains: peripheral joints (68 tender and 66 swollen joints, Health Assessment Questionnaire (HAQ), skin [Psoriasis Areas and Severity Index (PASI) and Dermatology Life Quality Index (DLQI)], enthesitis (Leeds Enthesitis Count and HAQ), dactylitis (number of tender dactylitic digits and HAQ), and spine (Bath Ankylosing Spondylitis Disease Activity Score (BASDAI) and Ankylosing Spondylitis QOL index (ASQoL). Within each domain, activity is graded as 0 (none), 1 (mild), 2 (moderate), and 3 (severe), according to predefined cut offs resulting a score ranging from 0-15. For modification of the CPDAI pain was incorporated using a pain VAS, and fatigue using the FACIT-fatigue. Cut offs between remission/ low disease activity, low/moderate, and moderate/high disease activity for the pain

VAS (10, 30 and 50 mm) were taken from the GRACE study (16) and for the FACIT-fatigue (15, 30 and 50mm) from the LOPAS II study (17). After the addition of pain and fatigue, the mCPDAI had a score range of 0-21.

The GRACE measure is derived from the tender and swollen joint count, HAQ, patient global, skin and joint VAS scores, PASI and Psoriatic Arthritis Quality of Life (PsAQoL). Scores are transformed into linear functions ranging from 0 (totally unacceptable state) to 1 (normal) based on established desirability functions. The eight transformed variables are then combined using the arithmetic mean GRACE= (1-arithmetic mean of variables) x 10. The pain VAS and FACIT-fatigue were also transformed into desirability functions and included in the arithmetic mean to give a modified version of the GRACE instrument (mGRACE) with the same 0-10 scale, where 0 is low and 10 high disease activity.

Psoriatic Arthritis Disease Activity Score (PASDAS) is a weighted index comprising assessments of joints, function (physical component summary scale of SF36, SF36_PF), acute-phase response (CRP), health related quality of life (QOL), also represented by the SF36_PF and patient and physician by Visual Analogue Scale (VAS) (16). The score range of the PASDAS is 0–10, with worse disease activity represented by higher scores.

The Disease Activity in Psoriatic Arthritis (DAPSA) was developed from a measure of Reactive Arthritis and is a measure of articular disease comprised of a joint count, patient global and pain scores, and CRP (18).

Sample Size and statistical analysis

A total of 128 patients was required to demonstrate equivalence between the two versions of the GRACE instrument, with a two-sided 90% confidence interval excluding a difference in means of more than 0.8 (the minimally important difference of the GRACE from the GRACE study). Using the same calculation based on the CPDAI gave a sample size of 84. Recruitment of a total of 141 patients allowed for a 10% drop out rate. The ability of each measure to detect those patients requiring treatment change was calculated using the independent samples ‘t’ statistic. Responsiveness of each measure following a change in medication was calculated using the standardised response mean (SRM, the mean difference before and after treatment change divided by the standard deviation of the difference) and magnitude of response using effect size (ES, the mean difference between scores divided by the pooled baseline standard deviation). Test re-test reliability was assessed using the Intra-Class Correlation method (ICC)

and Bland Altman method. Minimally Clinically Important Difference (MCID) was estimated using the anchor method.

RESULTS

ASSESS Results

Patient demographics are reported in Table 1. One hundred and forty-one patients completed 414 of a potential 423 individual study visits, but valid data were only available for 136 patients. Data to calculate all composite measures were available for 28 patients. Twenty-nine patients with stable disease had repeat clinical assessments, allowing test re-test reliability analysis.

In comparison with the CPDAI/mCPDAI, GRACE/mGRACE and DAPSA, the PASDAS was the best performing composite in all tests including responsiveness (SRM 0.84), magnitude of response (ES 0.62) or ability to detect treatment change (t-score 8.3), as shown in Table 2.

The mGRACE showed very similar performance characteristics to the GRACE with an unchanged ability to detect treatment change (t-score 7.8), marginally reduced responsiveness (SRM reduced from 0.67 vs 0.64) and increased effect size (ES 0.36 vs 0.44). The mCPDAI also had very similar characteristic to the CPDAI (Table 2) with a slightly increased ability to detect treatment change (t-score 6.8 vs 7.0), marginally reduced responsiveness (SRM 0.56 vs 0.46) and reduced effect size (ES 0.46 vs 0.36).

The ICC (95% CI) for tender and swollen joint counts were 0.94 (0.87-0.97) and 0.91 (0.80-0.96) respectively. The ICC for PASI was 0.95 (0.90-0.98). All composite measures demonstrated high levels of test-retest reliability with ICC >0.85, Table 2. The Bland Altman plots are shown in Figure 1 (19). The MCID for improvement was estimated based on eight individuals with a complete dataset to calculate all composites and who reported a ‘mild’ improvement in the severity of their PsA. MCID estimates were: for the CPDAI 0.5, PASDAS 1.2, GRACE 0.3 and DAPSA 7.2.

GRAPPA discussion session

Dr. Tillett introduced the session reviewing the need for a continuous composite measures and the existing candidate measures including the CPDAI, PASDAS, DAPSA and GRACE. The benefits and limitations of continuous composite measures, barriers to wider uptake and proposed modifications from the GRAPPA 2019 Paris meeting were reviewed (20). The historic lack of patient involvement in the development of composite measures and the relatively poor representation of outcomes important to patients such as pain and fatigue were also reviewed (14,21) as well as the role of the PSAID as an instrument to assess impact of disease in PsA and the rationale for separate measurement of disease activity and disease impact (22,23). At the GRAPPA 2019 Paris annual meeting, 76% of members supported the separate assessment of impact using the PSAID but also supported testing of the addition of pain and fatigue to the CPDAI and GRACE measure to determine the effect on the instruments performance (11).

Dr. Helliwell reviewed the ASSESS study methods used to incorporate pain and fatigue and the development of cut-off values for the pain VAS and FACIT-fatigue into the mCPDAI and mGRACE. He also reviewed the methods for assessing discrimination (SRM), decision to change treatment (t-score) and magnitude of response (Effect Size). The results of the ASSESS study for the performance characteristics of the PSADAS/ DAPSA and MDA were presented. A recommendation not to include pain and fatigue in the GRACE/ CPDAI and to support the PASDAS as the GRAPPA recommended composite and MDA as the target for clinical trials was presented.

Comments from the discussion included:

- Why are we not including pain and fatigue in composites, is it because they are not important? The authors and other members discussed the importance of measuring pain and fatigue as a high priority, however the data from the ASSESS study indicates that inclusion in the CPDAI and GRACE did not enhance their performance characteristics, and in some instances reduced them, leading to the view that pain and fatigue may be best measured in the PSAID (a measure of impact that can be affected by external non-disease factors) and not included in an composite measure of activity.
- Should PsA be treated to a dual target- biological remission measured by a composite measure of disease activity and remission for patient perspective (perhaps by the PSAID)? The authors and other members agreed this could be a new approach, particularly allowing focus on fatigue with non-pharmacological interventions.

- Why are we not recommending the DAPSA for clinical trials? This is due to the superior performance of the PASDAS to discriminate between treatment groups, seen in the ASSESS study data as well at the SEAM-PsA trial (24) where the PASDAS but DAPSA was able to discriminate between treatment arms (25).
- What about a composite for clinical practice? The authors agreed that different, more feasible composites for clinical practice were required and these are addressed in a second set of analyses, discussion and voting.
- What about axial disease in PsA? The authors highlighted that an improved definition of axial PsA was needed and then outcomes can be tested.

Members went on to vote on composite measures modifications and targets for clinical trials, the results are summarised in Table 3.

DISCUSSION

We report the performance characteristics of modified CPDAI and GRACE with the addition of pain and fatigue and comparison with the PASDAS, DAPSA and original versions. Modifications did not enhance the ability of the GRACE or CPDAI to detect change and in some instances reduced it. The PASDAS was the best performing continuous composite measure in terms of ability to detect treatment change, magnitude of response and responsiveness. Members voted that the PASDAS should be the GRAPPA recommended composite for clinical trial and MDA the treatment target.

Discussion during the composite session highlighted the importance of pain and fatigue and patient centred priority outcomes. There was recognition of the need to measure biological disease activity and the impact of disease on an individual (influenced by activity and external factors) and members voted that it is desirable to measure activity and impact separately (23).

An important consideration for continuous composite measure of disease activity are the philosophical advantages and disadvantages of combining different disease domains (joint/skin/ entheses) in a single measure. In our view there is a need to assess individual disease domains separately in clinical trials in order to detect differential response to therapy on the individual domains of joint, skin and nail, entheses, axial disease and dactylitis. However, a continuous composite provides additional information, providing an estimate of change in the overall disease burden in a single numeric value with contributions from both patient and

physician. Such a global estimate of disease cannot be achieved with individual domain assessments or patient reported outcome measures (PROMS) alone and a composite measure of disease activity fills this need.

There are number of strengths to this study design. We chose the modifications to be tests with a foundation of qualitative work that identified, prioritised and ranked outcomes and then mapping them to the existing composite measures (12,13). The modifications to be tested were voted by a global network of clinicians, patient research partners and industry stakeholders (11). The primary limitation to this study is missing data. While the proportion of missing data for any individual outcome was trivial, the total number of cases with complete data for all composites was small.

CONCLUSION

In summary, we report the performance characteristics of continuous composite measures of disease activity in PsA including the PASDAS, DAPSA, CPDAI, GRACE and modified versions of the CPDAI and GRACE with the addition of pain and fatigue. Modifications to the CPDAI and GRACE did not enhance their ability to detect change, and members voted for pain and fatigue to be measured separately in the PsAID. The PASDAS had the best performance characteristics and was voted by members to be the GRAPPA recommended composite measure for clinical trials with MDA as the treatment target.

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Figure 1. Bland Altman plots for each composite measure in test-retest. **Key:** Psoriatic Arthritis Disease Activity Score (PASDAS). Composite Psoriatic Arthritis Disease Activity Index (CPDAI) and Modified CPDAI- (mCPDAI). Disease Activity of Psoriatic Arthritis (DAPSA)

Supplementary file 1

Videos of the Composite sessions from the GRAPPA 2020 virtual annual meeting

Introduction:

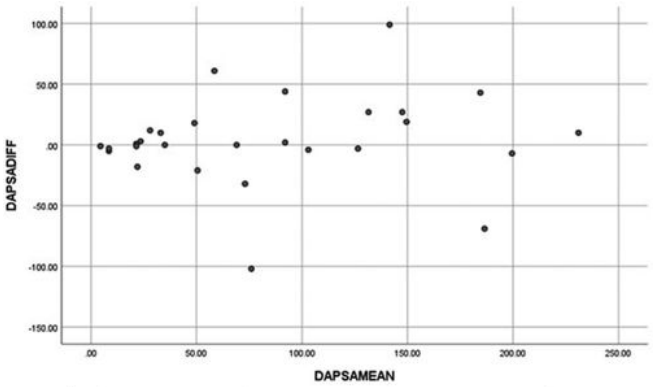
W. Tillett, https://youtu.be/BFvwKxLplXg

Results:

P. Helliwell, https://youtu.be/24eCIaBMADQ

Panel Discussion:

O. FitzGerald, P. Helliwell, W. Tillett, https://youtu.be/t2GZr_bwPiM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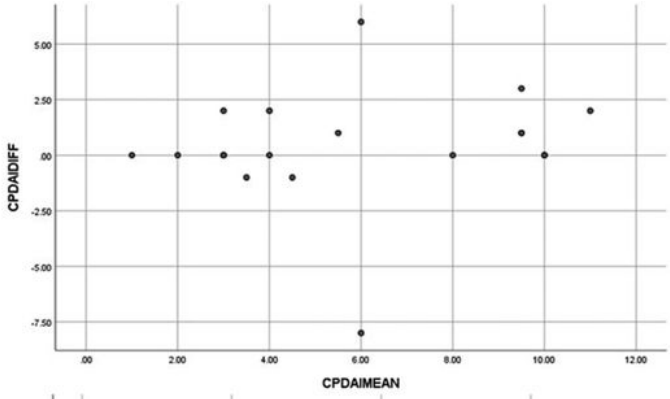
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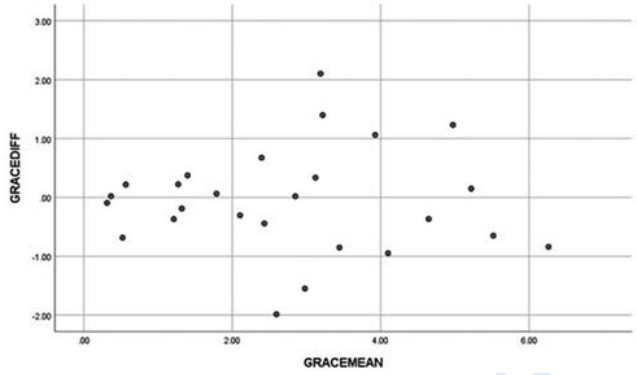
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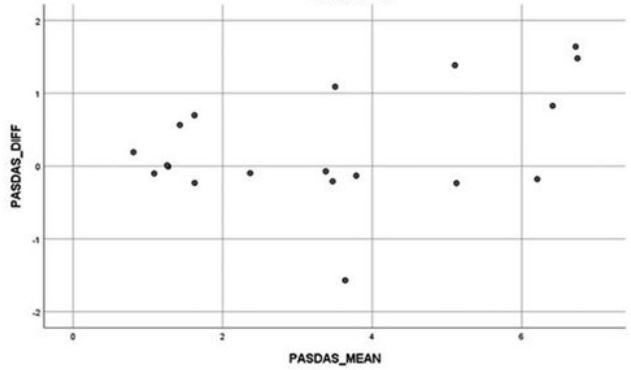
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0
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0
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4
6
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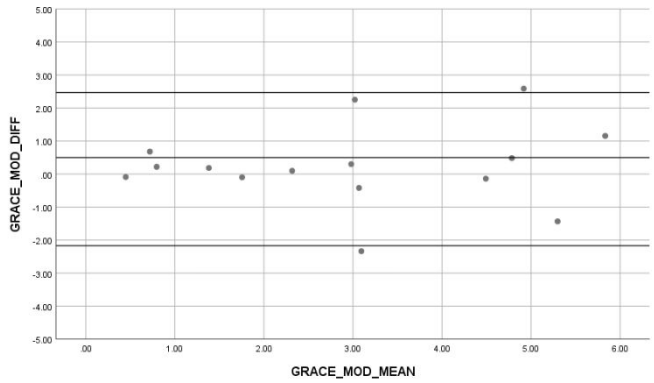
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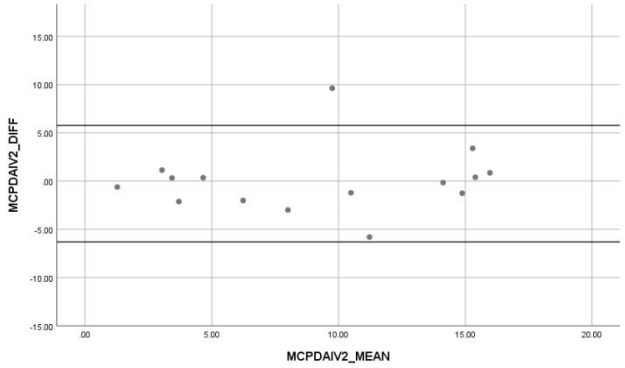
3.00
4.00
5.00
6.00
GRACE_MOD_MEAN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20.00
MCPDAIV2_MEAN

Table 1. Demographics of 136 patients with psoriatic arthritis recruited in the ACCESS study

Outcome	Mean (SD) values		
	All (n=136)	Treatment change (n=63)	No Treatment change (n=73)
Age: y	52.5 (13.6)	50.2 (14.0)	54.3 (13.1)
Gender: (M, F)*	59, 77	25, 38	34, 39
Disease Duration: y	4.0 (6.2)	2.9 (4.8)	4.9 (7.0)
Tender joint count: 0 – 68	9.6 (11.8)	13.1 (11.6)	6.3 (11.1)
Swollen joint count: 0 – 66	3.0 (4.1)	4.2 (4.0)	1.9 (3.8)
PASI: 0 - 72	1.4 (2.0)	1.6 (2.2)	1.2 (1.9)
Enthesitis count: 0 - 6	0.9 (1.5)	1.3 (1.8)	0.5 (1.0)
Dactylitis count: 0 - 20	0.3 (0.9)	0.4 (1.1)	0.2 (0.7)
Global VAS: 0 - 100	48.0 (29.0)	64.8 (20.7)	35.6 (28.6)
HAQ: 0 - 3	0.8 (0.7)	1.0 (0.7)	0.7 (0.7)

*Frequency

Abbreviations: F, Female; HAQ, Health Assessment Questionnaire; LDI, Leeds Dacylitis Index; LEI, Leeds Enthesitis Index; M, Male; PASI, Psoriasis Areas Severity Index; SD, standard deviation; VAS, Visual Analogue Scale; y, year

Table 2: Composite Score responsiveness, magnitude of response and ability to detect treatment change.

Composite (n=28)	SRM	Effect Size	T Score	ICC (95% CI)
PASDAS	0.84	0.62	8.3	0.93 (0.78 – 0.98)
DAPSA	0.56	0.44	7.4	0.81 (0.44 – 0.94)
CPDAI	0.54	0.46	6.8	0.88 (0.65 – 0.96)
mCPDAI	0.46	0.36	7.0	0.92 (0.76 – 0.97)
GRACE	0.67	0.36	7.8	0.87 (0.62 – 0.96)
mGRACE	0.64	0.44	7.8	0.89 (0.68 – 0.96)

Abbreviations: CI, confidence internal; CPDAI, Composite Psoriatic Arthritis Disease Activity Index; DAPSA, Disease Activity of Psoriatic Arthritis; GRACE, GRAPPA Composite Exercise; ICC, Intra-Class Correlation; mCPDAI, modified CPDAI; PASDAS, Psoriatic Arthritis Disease Activity Score; SRM, Standardised Response Mean.

Table 3. Voting results on composite measures for clinical trials

Question	Yes	No	Undecided
Pain and Fatigue are represented in the impact measure the PSAID. 76% GRAPPA members agree impact should be measured separately from disease activity. Data from the ASSESS study indicates incorporation of pain and fatigue to the CPDAI or GRACE does not enhance their ability to detect status (in terms of requiring treatment escalation), nor responsiveness. *Do you agree that pain and fatigue should not be included in modified composite measure?*	77%	6%	17%
The PASDAS received the most votes in the expert consensus exercise in 2018 ahead of the GRACE, CPDAI and DAPSA. The PASDAS has been shown to be the highest t score, effect size and responsiveness in the ASSESS study and clinical trial datasets. Modifications to the CPDAI and GRACE do not improve performance. *Do you agree that the PASDAS should be the GRAPPA recommended composite for use in clinical trials?*	82%	9%	9%
The MDA was developed as a target for treatment representing low disease activity. The MDA has been shown to discriminate between treatment arms in clinical trials and treatment strategy trials, correlate with LDA and remission states defined by continuous measures and correlate with reduced radiographic progression in real world cohorts. *Do you agree that the MDA should be the GRAPPA recommended target for use in clinical trials?*	90%	6%	4%

Supplementary Table 1. Questionnaires and application of Patient Reported Outcome Measures (PROMS) to different composites.

Questionnaire	Information gathered	For which composite
Background information	Background Information	n/a
Psoriatic Arthritis Impact of Disease (PSAID)	Impact of Disease	n/a
Work Productivity and Activity Index (WPAI)	Work data	n/a
Health based anchor questions	To estimate Minimally Important Difference (MID)	
Health Assessment Questionnaire (HAQ)	Physical Function	CPDAI, GRACE
European Quality of Life 5 Domain EQ5D	Quality of Life	CPDAI
Short Form Heath Questionnaire (SF36)	Quality of Life	PASDAS
Dermatology Life Quality Index (DLQI)	Skin specific Quality of Life	CPDAI
Functional Assessment of Chronic Illness (FACIT-Fatigue)	Fatigue	Modified CPDAI/ GRACE
Pain Visual Analogue scale (VAS)	Pain	Modified CPDAI/ GRACE
Physician/ Patient VAS	Global	PASDAS
Skin/ Joint Global scores VAS	Domain specific activity	Modified CPDAI/GRACE
Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)	Spinal Disease	CPDAI
Ankylosing Spondylitis Quality of Life (ASQoL)	Spinal specific Quality of Life	CPDAI
PsA Flare questionnaire	Flare	

Psoriatic Arthritis Quality of Life (PsAQoL)	PsA specific QoL	GRACE

Abbreviation: n/a, not applicable

Supplementary Table 2. Criteria for what constitutes medication change.

Medication	Considered a medication change	Not considered a medication change
Conventional synthetic Disease Modifying Anti Rheumatic Drug (csDMARD), anti-TNF, Glucocorticoid (im, po, iv)	Initiation, any dose increase, Switch from oral to subcutaneous MTX (increased bioavailability), Switch to or between anti-TNF	Dose reduction, Switch due to adverse events, Switch to biosimilar