Composite Disease Activity and Responder Indices for Psoriatic Arthritis: A Report from the GRAPPA 2013 Meeting on Development of Cutoffs for Both Disease Activity States and Response

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ABSTRACT. ***Objective.*** There are several new composite indices for assessing disease activity in psoriatic arthritis (PsA). Each may function as a disease state variable and a responder index. The aim of our study was to determine cutoffs for disease activity and response.

Methods. Data from the Group for GRAPPA Composite Exercise (GRACE) study were used to develop cutoffs using a number of different approaches. Voting on choice of cutoff was undertaken at the 2013 GRAPPA Annual Meeting in Toronto, Ontario, Canada.

Results. After voting, results for cutoffs for low/high disease activity for the Psoriatic ArthritiS Disease Activity Score (PASDAS), GRAppa Composite scorE (GRACE index), and Composite Psoriatic Disease Activity Index (CPDAI), respectively, were 3.2/5.4, 2.3/4.7, and 4/8. The measurement error for each composite score was estimated at 0.8, 1, and 2 for PASDAS, GRACE, and CPDAI, respectively.

Conclusion. Response criteria for the new composite indices have been developed. These now require further validation and testing in other datasets. (J Rheumatol 2014;41:1212–7; doi:10.3899/jrheum.140172)

Key Indexing Terms:
PSORIATIC ARTHRITIS
COMPOSITE DISEASE ACTIVITY INDEX
OUTCOME MEASURES
RESPONSE MEASURE

Psoriatic arthritis (PsA) is a heterogeneous disease that can manifest in several ways including arthritis, enthesitis, dactylitis, axial disease, and skin/nail involvement. For the last 12 years the primary outcome measure used in interventional studies has been the American College of Rheumatology 20% improvement (ACR20) criteria, a measure originally developed for rheumatoid arthritis (RA) that focuses on peripheral joint activity[1]. The ACR improvement criteria measure improvement in tender and swollen joint counts plus at least 3 of the following 5 measures: acute-phase reactant, patient global assessment of disease activity by visual analog scale (VAS), physician global (MD global) assessment of disease activity by VAS, pain by VAS, and physical function using the Health Assessment Questionnaire (HAQ). The ACR20, 50, and 70 scores refer to ≥ 20/50/70% improvements.

In addition, a number of studies have used the Disease Activity Score for 28 joints (DAS28)[2]. The DAS28 in RA measures 28-joint tender and swollen counts, patient global, and either erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). However, in PsA, the number of joints assessed should optimally include a 68-tender, 66-swollen joint count, which includes the distal interphalangeal (DIP) joints of the fingers. The 28-joint count excludes the DIP joints of the fingers, as well as the ankles and feet. Although the DAS28 has been shown to be capable of distinguishing between patients with PsA treated with anti-tumor necrosis factor agents from those receiving placebo, it was noted that 25% of the patients would not have been included in this study if a 28-joint count had been part of inclusion criteria[3]. Further, in cases of oligoarthritis, use of the DAS28 can misclassify 20% of cases, as shown in a cross-sectional dataset[4].

The Psoriatic Arthritis Response Criteria (PsARC) were developed for a specific Veterans Administration study of sulfasalazine in PsA but have been used widely in subsequent clinical trials[5]. To achieve response, a patient had to achieve 2 of the following, 1 of which had to be a joint count, and no worsening of any measure: ≥ 30%

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improvement in tender or swollen joint count; and 1-point improvement (on 5-point Likert scale) on patient global or MD global.

Several other candidate composite measures have been proposed, some of which capture aspects of PsA other than the peripheral arthritis. These include measures developed in the GRAppa Composite scorE (GRACE project); the Psoriatic Arthritis Disease Activity Score (PASDAS) and the Arithmetic Mean of Desirability Function (AMDF)[6]; the Composite Psoriatic Disease Activity Index (CPDAI)[7]; and the Disease Activity score for PSoriatic Arthritis (DAPSA)[8]. Initial comparison of these measures was made in the development phase of the PASDAS and AMDF[2] and other comparisons have been made using interventional trial data[9].

Composite indices may function in different ways. Responder indices, such as ACR20 in RA, measure changes in disease states with treatment interventions. Disease activity indices, such as the DAS28 in RA, measure both disease activity at a single time point and changes in disease activity after treatment interventions, thereby functioning both as a static measure of disease activity and a responder index, with cutoffs for disease activity states and magnitude of response.

At the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) annual meeting in Toronto, Ontario, Canada in July 2013, data were presented on the development of cutoffs for disease activity and response criteria for these new measures, and votes were taken to finalize the process.

METHODS

The GRACE study was a large observational study of 503 patients with PsA with data collected at 32 centers worldwide affiliated with GRAPPA. A large range of clinical data and patient-reported outcomes were collected at baseline, 3 months, 6 months, and 12 months. At each visit, treatment changes were noted, which were used as a surrogate for an active disease state. A change equated to additions of medication, dose increases of current medications, and/or changes to different medications. If treatments were changed because of an adverse event, cases were excluded from the "changed medication" group. Further descriptions and formulas for the composite measures are presented below.

Psoriatic Arthritis Disease Activity Score. The PASDAS is a weighted index comprising assessments of joints, function, acute-phase response, quality of life (QOL), and patient and physician MD by VAS. It is represented by the formula:

$$\text{PASDAS} = (((0.18 \times \sqrt{\text{Physician global VAS}}) + (0.159 \times \sqrt{\text{Patient global VAS}}) - (0.253 \times \sqrt{\text{SF36 – PCS}}) + (0.101 \times \text{LN (Swollen joint count + 1)}) + (0.048 \times \text{LN (Tender joint count + 1)}) + (0.23 \times \text{LN (Leeds Enthesitis Count + 1)}) + (0.377 \text{ LN (Dactylitis count + 1)}) + (0.102 \times \text{LN (CRP + 1)}) + 2)*1.5$$

where LN = natural logarithm, PCS = physical component summary scale of SF36, CRP = C-reactive protein in mg/l, SF36 = Medical Outcomes Study Short Form-36. All VAS scores are 0–100 mm. Swollen joint count is 66 joints, and tender joint count 68. The score range of the PASDAS is 0–10, with worse disease activity represented by higher scores.

Arithmetic mean of the desirability function and GRACE index. The AMDF is a composite score comprising assessments of joints, skin, pain, function, and health-related QOL. Each domain was rated by physicians on a similar "desirability" scale to be able to combine all the items, and transformed into a 0–1 scale where 0 is a completely unacceptable state and 1 is normal. The variables transformed were (1) 68 tender joint count, (2) 66 swollen joint count, (3) HAQ, (4) Patient global assessment of disease activity by VAS, (5) Patient VAS for skin, (6) Patient VAS for joints, (7) Psoriasis Area and Severity Index (PASI), and (8) Psoriatic Arthritis QOL Index (PsAQoL).

The 8 transformed variables were combined using the arithmetic mean. For the purposes of this analysis, as agreed at the GRAPPA meeting in Washington, DC, in November 2012, the AMDF was transformed, and renamed, as follows:

$$\text{GRACE index} = (1 - \text{AMDF}) \times 10$$

This provides a score range of 0–10, where 0 is best and 10 is worst.

Composite Psoriatic Arthritis Disease Activity Index. The CPDAI measures disease activity in 5 domains: peripheral joints (68 tender and 66 swollen joints, and HAQ), skin [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 and Ankylosing Spondylitis QOL index)[7]. Within each domain, severity was graded as 0 (none), 1 (mild), 2 (moderate), and 3 (severe), according to predefined cutoffs.

Disease Activity Score for Rheumatoid Arthritis. The DAS28 in RA includes 28-joint tender and swollen counts, patient global VAS score, and either ESR or CRP. The score is calculated using weighting of the components, and ranges between 0 and 10. The DAS28 was calculated as follows:

$$\text{DAS28} = (0.56 \times \sqrt{\text{tender joint count}}) + (0.28 \times \sqrt{\text{swollen joint count}}) + (0.36 \times \text{LN (CRP+1)}) + (0.014 \times \text{global health VAS}) + 0.96$$

Disease Activity Index for Psoriatic Arthritis. The DAPSA measures disease activity in peripheral arthritis using 68 tender and 66 swollen peripheral joint counts, patient global VAS (0–10 scale), patient pain VAS (0–10 scale), and CRP. The composite score is a simple sum of the scores[8].

Development of cutoffs for disease activity. As there is no single acceptable "gold standard" for low and high disease activity, 3 methods were used to estimate cutoffs: (1) physician and patient global scores; (2) score distribution method; and (3) receiver-operating curve (ROC) method. In addition, the interperiod correlation coefficient was used to estimate "e," the measurement error.

The results were to be interpreted using a consensus approach with experts in the field. A voting system was used to arrive at cutoffs for each scoring system.

Physician and patient global scores. Physician and patient global scores were the external standards, with which the following cutoffs were used: < 10 low disease activity; ≥ 10 but < 30 moderate; ≥ 30 but < 60 high; ≥ 60 very high. Using these cutoffs, and the ROC curves generated with them, selection of the cutoff was made at the 90% specificity value, in order not to misclassify patients by keeping the false-positive rate low.

Score distribution method. An estimation of cutoffs for disease activity based on the distribution of scores of people in high and low disease activity was used, based on the methods described in the development of cutoffs for the DAS score[10]. The score distributions for the PASDAS, taken from the GRACE dataset, are shown in Figure 1. Considerable overlap can be seen in scores between the low and high disease activity states. For this reason, a 50th percentile cutoff for both low and high distributions was chosen.

ROC method. This approach used a definition of high disease activity (in GRACE, the physician's decision to escalate treatment) and constructed ROC curves from which the cutoff for high disease activity can be estimated, using a cutoff at 90% specificity (Figure 2).

Estimation of measurement error. As with the DAS score, an estimate of

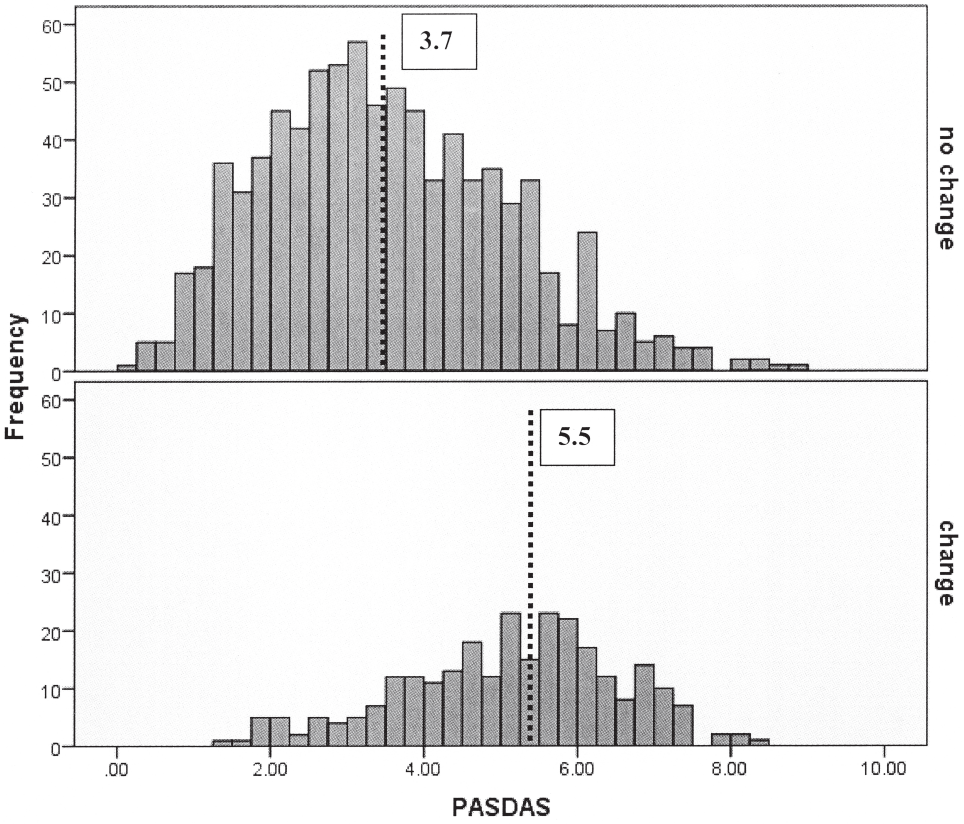

Figure 1. Score distributions for PASDAS in GRACE study. The "change" group had its treatment changed or escalated for "active" disease. The "no change" group did not have treatment change and was therefore deemed to be in stable disease activity. The broken lines represent the 50th percentile values. PASDAS: Psoriatic ArthritiS Disease Activity Score; GRACE: GRAppa Composite scorE (index).

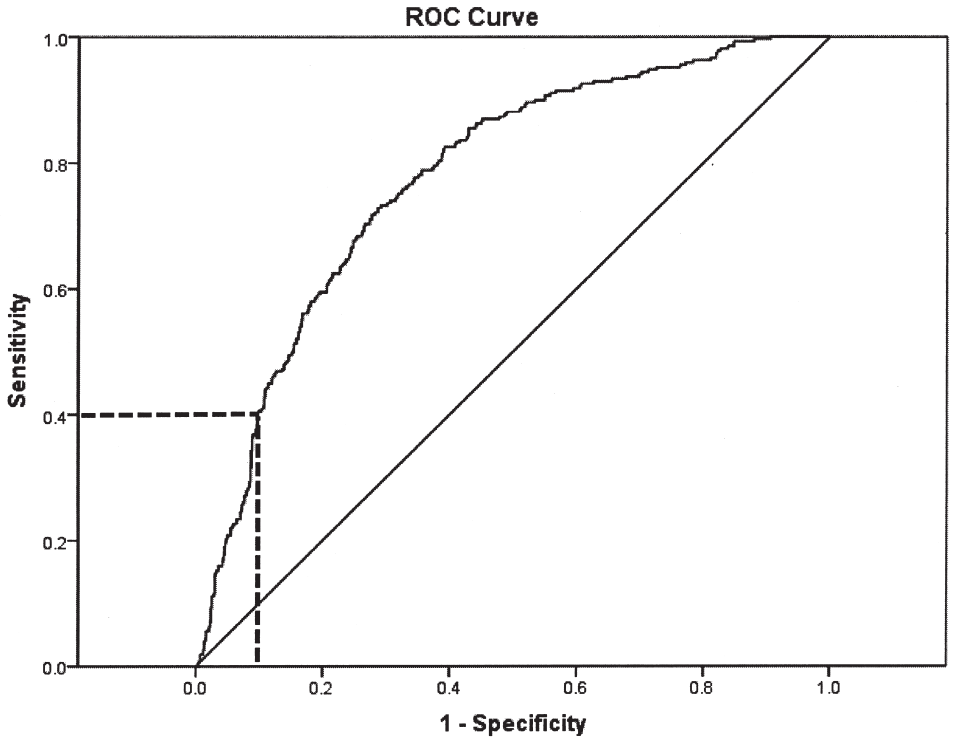

Figure 2. Receiver-operating curve (ROC) for PASDAS with decision to change treatment as discriminator. The value of PASDAS at 90% specificity was 5.62 (at this point sensitivity was 40%, as indicated by the dotted line). Area under the curve was 0.78 (95% CI: 0.75–0.81). PASDAS: Psoriatic ArthritiS Disease Activity Score.

measurement error (e) was obtained from the interperiod correlation coefficients for each measure using data from each of the assessment points in the GRACE study[6]. The value of e is represented by:

$$e = \sqrt{(sd^2)}\ (1/r_o - 1)$$

where sd = standard deviation of measure, and r_o is derived from the regression of the interperiod correlation coefficients. A "good" response is represented by (2e).

Consensus approach and voting. The results of this exercise and choice of cutoff were debated at the GRAPPA Annual Meeting in 2013. After discussion, GRAPPA members were asked to vote on the following question: Should the cutoffs be based on (1) lower estimate (patient); (2) upper estimate (physician); or (3) middle point between these 2 (i.e., mean)?

RESULTS

The GRACE database obtained data at baseline, 3 months, 6 months, and 12 months. At each timepoint the physician was asked about treatment change, which therefore provided more data points than the baseline recruitment figures (n = 503). The total number of timepoints at which change was recorded varied according to outcome measures owing to missing data: PASDAS 1103 data points, GRACE 1377, CPDAI 1356, DAS28 1143, and DAPSA 1143.

Physician and patient global scores. For illustration, global scores are provided for the PASDAS in Table 1. The discrepancy between the cutoffs based on physician global scores and those based on patient global scores was resolved by selecting the patient global scores (as agreed at the GRAPPA meeting in November 2012). The process was repeated for all 5 measures (see column 4, Table 2).

Score distribution method. Percentiles were calculated for each measure according to the score distribution for active and inactive disease; they are shown in Table 3. Because of the overlap mentioned in Methods, the 50th percentile was chosen as the cutoff for each distribution, representing high and low disease activity, as shown in column 6, Table 3. The 50th percentile cutoffs are also shown in column 2, Table 2.

ROC method. This approach used the definition of high disease activity (the decision to escalate treatment) to construct ROC curves from which the cutoff for high disease activity could be made. These are shown in column 3, Table 2.

Definition of response. Results of the regression of the inter-

Table 1. Cutoffs for disease activity for PASDAS using physician and patient global scores.

Score	Cutoff		
	Low (sens, spec)	Moderate (sens, spec)	High (sens, spec)
Physician global	3.59 (73.2, 90.2)	4.44 (83.6, 90.0)	5.65 (80.8, 90.0)
Patient global	2.67 (84.4, 90.2)	3.67 (81.3, 90.0)	5.07 (71.1, 90.0)

PASDAS: Psoriatic ArthritiS Disease Activity Score; Low: cutoff between low and moderate disease activity; Moderate: cutoff between moderate and high disease activity; High: cutoff between high and very high disease activity; sens, spec: sensitivity, specificity.

Table 2. Cutoffs for disease activity in composite measures.

Measure		Score Distribution			
		50th Percentile	ROC	VAS Global	Mean*
Column No.	1	2	3	4	5
PASDAS	Low	3.7	N/A	2.7	3.2
	Mod	N/A	N/A	3.7	N/A
	High	5.5	5.6	5.1	5.4
GRACE	Low	3.0	N/A	1.6	2.3
	Mod	N/A	N/A	2.9	N/A
	High	4.6	5.2	4.3	4.7
CPDAI	Low	4	N/A	4	4
	Mod	N/A	N/A	6	N/A
	High	7	8	8	8
DAS28-CRP	Low	2.8	N/A	2.7	2.8
	Mod	N/A	N/A	3.3	N/A
	High	3.9	4.7	4.1	4.2
DAPSA	Low	18.5	N/A	18.5	18.5
	Mod	N/A	N/A	31.2	N/A
	High	33.1	55.2	47.0	45.1

*Mean of estimates (50th percentile, ROC, and VAS global). CPDAI: Composite Psoriatic Disease Activity Index; DAPSA: Disease Activity score for PSoriatic Arthritis; DAS28-CRP: Disease Activity Score for 28 joints–C-reactive protein; GRACE: GRAPPA Composite Exercise; GRAPPA: Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; N/A: not available; PASDAS: Psoriatic ArthritiS Disease Activity Score; ROC: receiver-operating curve; VAS: visual analog score.

Table 3. Percentiles for each score distribution.

Measure		Percentile 5	10	25	50	75	90	95
PASDAS	No change	1.30	1.70	2.67	3.66	4.91	6.10	6.51
	Change	2.96	3.61	4.49	5.45	6.19	6.89	7.14
GRACE	No change	0.57	0.78	1.54	2.95	4.32	5.41	6.26
	Change	1.20	2.23	3.42	4.57	5.68	6.60	7.16
CPDAI	No change	1.00	2.00	3.00	4.00	7.00	9.00	10.00
	Change	2.00	3.00	5.00	7.00	9.00	10.00	11.00
DAS28-CRP	No change	1.34	1.50	1.94	2.83	3.74	4.98	5.72
	Change	1.82	2.16	3.09	3.88	4.76	5.57	5.70
DAPSA	No change	2.80	4.55	9.48	18.45	32.83	60.75	107.60
	Change	7.01	14.40	22.30	33.10	55.25	72.27	105.81

CPDAI: Composite Psoriatic Disease Activity Index; DAPSA: Disease Activity score for PSoriatic Arthritis; DAS28-CRP: Disease Activity Score for 28 joints–C-reactive protein; GRACE: GRAPPA Composite Exercise; GRAPPA: Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; PASDAS: Psoriatic ArthritiS Disease Activity Score.

period correlation coefficients are shown in Table 4. The value of e is the measurement error (see Methods) and a good response is represented by (2e).

Triangulation of results. Combining the various estimates of the cutoffs, together with the estimates of good response, the results are summarized for all 5 measures in Table 2. Note that the cutoffs determined for the DAS28 are different from those defined for RA. It is also clear from Table 2 that some of the estimates differ. Where discrepancies were found, the choice of cutoff was determined by consensus (see Methods). Voting results were as follows: patient-derived values, 29%; physician-derived, 12%; and a mean of those values, 59%. The mean value of the cutoff is shown in Table 2, column 5.

DISCUSSION

Data from the GRACE study have been used, in a manner similar to the development of the DAS (European League Against Rheumatism response criteria), to define activity states and response criteria for the new composite measures that take a more comprehensive account of PsA. A number of choices for cutoffs were available. A process of triangulation was undertaken to cross-validate estimates. The main discrepancies in the estimates occurred for the PASDAS and GRACE measures. The discrepancies resulted from the different methodological approaches — the patient-based methods (using the global VAS) gave estimates that were lower than the physician-based methods (using the decision to change treatment). In these discrepant cases, voting by GRAPPA members resulted in a majority for using the mean value of available estimates as cutoffs for disease activity and response.

What would PsA response criteria look like? These are indicated in Table 5, but require further evaluation in interventional studies. The defined low disease activity states may also be used as specific targets for treatment in PsA, both in clinical practice and clinical trials. No matter which

Table 4. Results of regression using interperiod correlation coefficients.

Measure	r_o	SD	e	R^2
PASDAS	0.826	1.69	0.776	0.734
GRACE	0.782	1.88	0.989	0.459
CPDAI	0.692	2.78	1.853	0.533
DAS28-CRP	0.755	1.34	0.763	0.660
DAPSA	0.827	31.08	14.215	0.892

r_o: derived from the regression equation of the interperiod correlation coefficients and represents the correlation at time zero; SD: standard deviation of r_o; e: measurement error; R^2: measure of goodness of fit of regression equation; CPDAI: Composite Psoriatic Disease Activity Index; DAPSA: Disease Activity score for PSoriatic Arthritis; DAS28-CRP: Disease Activity Score for 28 joints–C-reactive protein; GRACE: GRAPPA Composite Exercise; GRAPPA: Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; PASDAS: Psoriatic ArthritiS Disease Activity Score.

Table 5A. Response criteria for the Psoriatic ArthritiS Disease Activity Score (PASDAS).

Final PASDAS Score	Improvement > 1.6	< 1.6 but > 0.8	< 0.8
≤ 3.2	1	2	3
> 3.2 but < 5.4	2	2	3
≥ 5.4	2	3	3

1: good response; 2: moderate response; 3: poor response.

Table 5B. Response criteria for the GRAPPA Composite Exercise (GRACE).

Final GRACE Score	Improvement > 2.0	< 2.0 but > 1.0	< 1.0
≤ 2.3	1	2	3
> 2.3 but < 4.7	2	2	3
≥ 4.7	2	3	3

1: good response; 2: moderate response; 3: poor response.

Table 5C. Response criteria for the Composite Psoriatic Disease Activity Index (CPDAI).

Final CPDAI Score	Improvement		
	> 4.0	< 4.0 but > 2.0	< 2.0
≤ 4.0	1	2	3
> 4.0 but < 8.0	2	2	3
≥ 8.0	2	3	3

1: good response; 2: moderate response; 3: poor response.

Table 5D. Response criteria for Disease Activity Score (DAS28-CRP).

Final DAS28-CRP Score	Improvement		
	> 1.6	< 1.6 but > 0.8	< 0.8
≤ 2.8	1	2	3
> 2.8 but < 4.2	2	2	3
≥ 4.2	2	3	3

1: good response; 2: moderate response; 3: poor response. CRP: C-reactive protein.

Table 5E. Response criteria for Disease Activity score for PSoriatic Arthritis (DAPSA).

Final DAPSA Score	Improvement		
	> 28.4	< 28.4 but > 14.2	< 14.2
≤ 18.5	1	2	3
> 18.5 but < 45.1	2	2	3
≥ 45.1	2	3	3

1: good response; 2: moderate response; 3: poor response.

of these new composite indices is used, it will be important to be able to report the values for individual domains, as will the single composite score; otherwise, differential treatment responses (e.g., between the skin and the joints) will be missed. The single composite score will retain the additional power provided by including all relevant domains, but it will still be appropriate to provide data on the component parts. In time, it is hoped that shorter versions of these indices that function equivalently to the parent index will be developed; however, further experience with the full composite index is required before this can be done. For the moment, GRAPPA members suggest using the PASDAS, GRACE, or CPDAI; future studies will help determine which of these is preferable.

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