

# A New Disease Activity Index for Rheumatoid Arthritis: Mean Overall Index for Rheumatoid Arthritis (MOI-RA)

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**ABSTRACT. Objective.** To develop a continuous composite index of disease activity for rheumatoid arthritis (RA) based on the 7 American College of Rheumatology (ACR) core data set of disease activity measures: Mean Overall Index for Rheumatoid Arthritis (MOI-RA).

**Methods.** The MOI-RA is the mean of standardized values of tender and swollen joint counts (28, 42, or 66/68 joint counts), physical function (Health Assessment Questionnaire 0–3), patient’s and physician’s assessments of global health and patient’s assessment of pain (visual analog scale 0–100 mm) and erythrocyte sedimentation rate (1–100). All the 7 components were standardized (0–100), and the mean of standardized values was calculated. The range of MOI-RA is 0–100; higher values indicate poorer outcomes. The validity and measurement properties of MOI-RA were analyzed in 169 patients in the Finnish RA Combination therapy trial.

**Results.** The mean MOI-RA28 decreased from 38.5 to 13.3 [standardized response mean (SRM) = 1.8, effect size (ES) = 1.9] from baseline to 6 months, compared to Disease Activity Score (DAS) 28, which decreased from 5.55 to 2.77 (SRM = 2.0, ES = 2.8). Correlation between MOI-RA28 and DAS28 was 0.90. When compared to the ACR response categories (20/50/ACR remission), changes in MOI-RA versions (using 28/42/66 joints) were similar. The reproducibility of MOI-RA with different joint counts was 0.97. A simulation in which 15% of the component values of MOI-RA were randomly omitted indicated an intraclass correlation coefficient of 0.98 between incomplete and complete data.

**Conclusion.** MOI-RA is a simple and feasible index based on the ACR core data set of disease activity measures for assessment of disease activity and treatment response in RA trials and clinical settings. (First Release May 15 2008; J Rheumatol 2008;35:1522–7)

*Key Indexing Terms:*  
DISEASE ACTIVITY

RHEUMATOID ARTHRITIS  
COMPOSITE INDEX OF DISEASE ACTIVITY

The contemporary approach to treatment of patient with rheumatoid arthritis (RA) involves aggressive therapy with disease modifying antirheumatic drugs (DMARD) and biologic agents<sup>1-4</sup>. The goals of treatment are to prevent structural damage, functional impairment, work disability, and premature mortality. As no single measure can serve as the “gold standard” to assess patient status in RA as in hypertension or diabetes, a pooled index of several individual measures is required<sup>5</sup>. Regular assessments of disease activity can successfully be used in the clinic for guidance of treatment<sup>1,3</sup>. Indices are needed in randomized controlled trials (RCT) to demonstrate the efficacy of a new drug. Payers need disease activity measurements for RA to decide

whether to provide an expensive treatment to an individual patient.

Indices used in RCT to document the efficacy of a treatment for RA include the American College of Rheumatology (ACR) improvement criteria<sup>6</sup> (Table 1), later known as the ACR20 response and succeeded by higher thresholds for improvement, ACR50 and ACR70<sup>7</sup>. The Disease Activity Score (DAS)<sup>8,9</sup> and its modified version including 28 joints (DAS28)<sup>10</sup> provide European League Against Rheumatism (EULAR) response criteria. The ACR and EULAR response criteria are the current standards to monitor treatment response in RA clinical trials<sup>11</sup>. Minimal disease activity of RA can be assessed using definitions that are based on either DAS28 or the ACR core set criteria<sup>12</sup>.

Recently, additional composite indices have been presented: the Simplified Disease Activity Index (SDAI)<sup>13</sup> and the Clinical Disease Activity Index (CDAI)<sup>14</sup>. Both are based on a simple sum of the outcome measures: tender (TJC) and swollen (SJC) joint count based on 28 joints, patient global assessment of disease activity [visual analog scale (VAS) 0–10 cm], physician global assessment of dis-

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Table 1. ACR Core Set and ACR improvement criteria requirements.

ACR Core Set	ACR Improvement Criteria Requirements
Tender joints	≥ 20%
Swollen joints	≥ 20%
Patient's assessment of pain (VAS)	
Patient's global assessment of disease activity (VAS)	≥ 20% in 3 of the 5 measures
Physician's global assessment of disease activity (VAS)	
Patient's assessment of physical function	
Acute-phase reactant value	

ACR: American College of Rheumatology; RA: rheumatoid arthritis; VAS: visual analog scale.

ease activity (VAS 0–10 cm) and C-reactive protein (CRP is not included in CDAI). ACR-N<sup>15</sup>, the hybrid measure of ACR<sup>16</sup>, and other continuous indices<sup>17,18</sup> that are based on ACR core data set measures assess percentage change in disease activity instead of current disease activity. Indices that include only patient reported outcomes such as the patient activity score<sup>19</sup> also discriminate effectively between active and control treatments in clinical trials<sup>17,18,20</sup>.

All indices to assess disease activity in RA have some shortcomings. DAS includes 4 variables and it requires complex calculations like square root and logarithm. Further, DAS, SDAI, and CDAI do not include patient functional status [Health Assessment Questionnaire (HAQ)], which is the best predictor of most severe longterm outcomes of RA<sup>21–23</sup>. The ACR20/50/70 response criteria as well as ACR-N<sup>15,24</sup> or ACR Hybrid<sup>16</sup> are based on change in disease activity and do not allow assessment of the current disease activity and therefore cannot be used in cross-sectional settings. These considerations led us to develop a disease activity index based on all 7 core set components of the ACR response criteria for RA: Mean Overall Index for Rheumatoid Arthritis (MOI-RA), and to analyze its validity and measurement properties in the Finnish Rheumatoid Arthritis Combination therapy (FIN-RACo) trial.

## MATERIALS AND METHODS

**Reference population.** The FIN-RACo study<sup>25</sup> included 195 patients with recent onset RA who met the ACR criteria for RA<sup>26</sup> and had active disease, and were randomized to receive either DMARD combination therapy or DMARD monotherapy. The study has been described in detail<sup>25</sup>.

Baseline, 6 month, and 12 month data of the patients were analyzed. Clinical assessments included tender and swollen joint counts (28, 42, and 68/66 joint counts), physician and patient global assessments of global health and patient's assessment of pain on VAS (VAS 0–100 mm), physical function on patient self report (HAQ), and erythrocyte sedimentation rate (ESR).

**MOI-RA.** The MOI-RA is the mean of standardized values of tender and swollen joint counts (28, 42 or 66/68 joint counts); patient's (GH) and physician's (GL) assessments of global health, and patient's assessment of pain (VAS 0–100 mm), the HAQ (0–3), and ESR (1–100). In ESR, all values above 100 are replaced by value 100. Standardization means that the effect of an individual component on the total score is equal: HAQ value (range 0–3) is divided by its maximum, which is 3, and multiplied by 100. Similar calculations are performed with the other components: they are standardized to range from 0 to 100. The mean of the standardized values

is calculated. The range of MOI-RA is 0–100; higher values indicate poorer outcomes. If values of 1–3 components of MOI-RA are missing, standardized values are calculated from the available component values and the mean of the standardized values is recorded.

**DAS28.** DAS28 was calculated with formula

$$0.56 \times \sqrt{(\text{tender joints } 28)} + 0.28 \times \sqrt{(\text{swollen joints } 28)} + 0.70 \times \ln(\text{ESR}) + 0.014 \times \text{GH}^{27}$$

**Definition of remission.** The ACR remission criteria were defined as: no joint swelling or soft tissue swelling of tendon sheets, no joint tenderness or pain on motion, normal ESR of < 30 in women and < 20 in men, morning stiffness ≤ 15 min, absence of joint pain by history. The criterion of “no fatigue” was excluded, but the other 5 criteria had to be fulfilled.

**Criterion validity.** MOI-RA was compared both with ACR response criteria and DAS28. Mean change in MOI-RA from baseline to 6 months was calculated in patients who did not meet ACR20 response criteria, patients who met ACR20 but not ACR50 response, ACR50 but not ACR remission, and patients who met ACR remission criteria<sup>6,7</sup>.

**Sensitivity to change.** Sensitivity to change of the MOI-RA index was analyzed in the reference patient population from baseline to 6 months, and compared to DAS28.

**Stability of imputation.** Stability of imputation is a useful characteristic of an index when a data set is incomplete. To examine the stability of imputation of MOI-RA, a simulation was performed where 15% of the values were omitted (0–3 of 7 measures per patient lacking).

**Statistical analysis.** Descriptive statistics: The results are presented as mean or median, standard deviation (SD), and/or interquartile range (IQR). Distributions of MOI-RA and DAS28 are represented as skewness and kurtosis. Coefficient of variation was calculated for both indices using formula: (SD/mean value of index at baseline) × 100. Confidence intervals (95% CI) were obtained from bias corrected bootstrapping (5000 replications). Assumptions of normality in the baseline index values were evaluated by the Kolmogorov-Smirnov test with Monte Carlo p values. Internal consistency between components of MOI-RA was estimated by calculating Cronbach's alpha, and reproducibility of MOI-RA by calculation of intra-class correlation coefficient (ICC).

**Criterion validity:** Possible relationship between MOI-RA and different ACR response classes was studied using analyses of covariance. Agreement between MOI-RA and DAS28 was tested using Pearson's correlation coefficient.

**Responsiveness:** Responsiveness was calculated as standardized response mean (SRM) and effect size (ES). SRM was defined as the mean change of the score from baseline divided by the SD of this change<sup>28</sup>. ES was defined as the mean change from baseline divided by the SD of the baseline scores<sup>29</sup>. CI of ES and SRM values were obtained by bias corrected bootstrapping (5000 replications).

Sensitivity to change: To be able to include all information of the patient population at all timepoints (baseline, 6 and 12 mos) repeated measures analyses were performed by using generalized linear mixed models.

## RESULTS

**Patient demographics at baseline.** The reference patient population included 169 patients with complete ACR core set data at baseline, at 6 and 12 months; 79 patients were randomized to combination therapy arm, and 90 patients to monotherapy. The mean age of the patients was 47 years, 106 (63%) were women, 120 (71%) had positive rheumatoid factor, and 83 (49%) had erosions at baseline.

**Descriptive statistics of MOI-RA and DAS28 in the reference population.** Descriptive statistics and internal consistency are presented in Table 2. Coefficients of variation were higher in MOI-RA compared to DAS28. Assumptions of normal distribution were satisfied: DAS28 ( $p = 0.81$ ), MOI-RA28 ( $p = 0.71$ ), MOI-RA42 ( $p = 0.64$ ), and MOI-RA66/68 ( $p = 0.66$ ). The reproducibility between MOI-RA indices with different joint counts was 0.97 (95% CI 0.88–0.99).

**Criterion validity.** ACR20 and ACR50 response are a change score and not a continuous variable such as DAS and MOI-RA. Figure 1 illustrates mean baseline adjusted change in MOI-RA from baseline to 6 months in patients who did not meet the ACR20, who met ACR20 but not ACR50, ACR50 but not remission, and who met remission criteria. When compared to the ACR response categories (20/50), changes in MOI-RA versions (using 28/42/66 joints) were similar (Figure 1). The correlation between MOI-RA and DAS28 was between 0.84 and 0.90 (Table 3).

**Responsiveness and sensitivity to change.** The mean MOI-RA (SD) values at baseline with 28, 42, and 66/68 joint counts were 38.5 (13.6), 39.2 (13.3), and 35.6 (12.8), respectively, indicating a decrease in the MOI-RA values from baseline to 6 months of approximately 65%. The mean DAS28 (SD) at baseline was 5.55 (0.98), and a 50% decrease during the same time period was seen (Table 4). Sensitivity to change of MOI-RA and DAS28 is shown in Figure 2; both indices discriminate the 2 treatment arms sig-

nificantly. SRM and ES of both DAS28 and MOI-RA for all joint counts were excellent (Table 4).

**Stability of imputation.** A simulation in which 15% of the component values of MOI-RA were randomly omitted (0–3 of the 7 measures per patient could be missing) was performed: the ICC was 0.98 (95%CI: 0.97 to 0.99) between incomplete and complete data.

## DISCUSSION

In accordance with the ACR response criteria widely used in RCT<sup>30–33</sup>, MOI-RA is an index based on all 7 components of the ACR core set. MOI-RA has major advantages over the ACR20/50/70 response criteria: it is a continuous index and it enables the assessment of current disease activity and can therefore be used in cross sectional studies. By definition, MOI-RA can recognize worsening in clinical status, which is not possible with the ACR20/50/70 response criteria. Further, MOI-RA is easy to calculate compared to other indices that are based on the ACR core data set variables.

The content validity of MOI-RA is based on the fact that the assessed measures are included in the highly validated ACR core set of disease activity<sup>34</sup>. These criteria include important domains of the disease: those valued by clinicians, such as joint counts and laboratory tests, and those valued by the patients, such as pain and functional status. Criterion validity is based on the highly significant correlation of MOI-RA and DAS28, and relationship of the change in MOI-RA with different ACR response categories and ACR remission. Correlation of MOI-RA with SDAI and CDAI was not studied because those indices are not so widely used in RA studies as DAS28.

Expert rating versus response criteria to determine whether the criteria can adequately discriminate between patients with important clinical improvement and those without<sup>35</sup> was not regarded as necessary, as MOI-RA was examined against ACR20 and ACR 50 responses and ACR remission criteria<sup>36</sup>. In terms of responsiveness, ES > 0.8 are considered excellent<sup>37</sup>, and ES of MOI-RA and DAS28 are at least twice the value. The discriminative power of disease activity index is important in RCT. MOI-RA discriminated

Table 2. Distributions and internal consistency of MOI-RA and DAS28 at baseline.

	DAS28	MOI-RA28	MOI-RA42	MOI-RA66/68
Mean (SD)	5.55 (0.98)	38.5 (13.6)	39.2 (13.3)	35.6 (12.8)
Median (IQR)	5.53 (4.90, 6.17)	38.8 (28.7, 46.8)	38.6 (28.3, 47.1)	35.5 (26.5, 42.7)
Range	3.03–8.03	13.2–73.3	16.1–72.2	13.8–71.6
Coefficient of variation*, % (95% CI) <sup>‡</sup>	18 (16 to 20)	35 (32 to 39)	34 (31 to 37)	36 (32 to 39)
Skewness (95% CI)	0.12 (–0.17 to 0.37)	0.40 (0.18 to 0.64)	0.41 (0.21 to 0.67)	0.45 (0.23 to 0.69)
Kurtosis (95% CI)	2.9 (2.5 to 3.4)	2.8 (2.4 to 3.4)	2.7 (2.3 to 3.2)	2.8 (2.4 to 3.4)
Internal consistency <sup>†</sup> (95% CI)	0.49 (0.37 to 0.59)	0.78 (0.72 to 0.82)	0.80 (0.75 to 0.84)	0.80 (0.75 to 0.84)

\* (SD of the index at baseline/mean value of the index at baseline) × 100; <sup>†</sup> Internal consistency between components of MOI-RA was estimated by calculating Cronbach's alpha; <sup>‡</sup> Confidence interval obtained from bias corrected bootstrapping (5000 replications). MOI-RA: Mean Overall Index for Rheumatoid Arthritis; DAS28: Disease activity Score 28 joint count; SD: Standard deviation; IQR: interquartile range; CI: confidence interval.

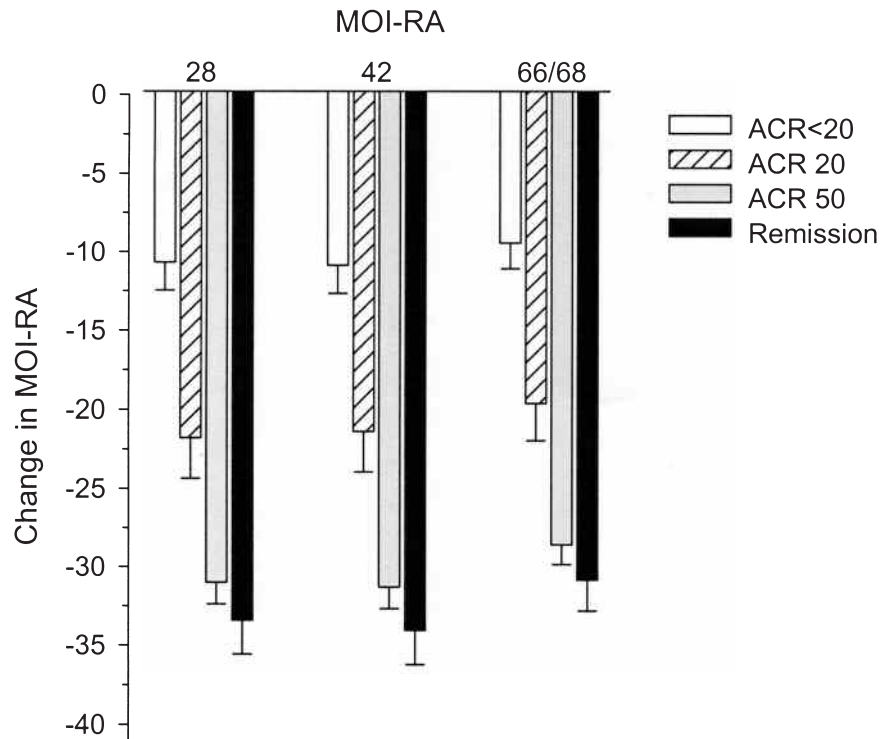


Figure 1. Changes in MOI-RA (28, 42 and 66/68 joint counts) in patients who did not meet the ACR 20 response, who met the ACR20, but not ACR50 response, and ACR50 response but not ACR remission and in patients who met ACR remission.

Table 3. Correlation\* between MOI-RA (with joint counts 28, 42, and 66/68) and DAS28.

	DAS28 (95% CI)	MOI-RA28 (95% CI)	MOI-RA44 (95% CI)
MOI-RA 28	0.90 (0.86 to 0.92)		
MOI-RA 42	0.86 (0.82 to 0.89)	0.99 (0.97 to 1.00)	
MOI-RA 66/68	0.84 (0.79 to 0.87)	0.98 (0.97 to 0.99)	0.99 (0.97 to 1.00)

\* Calculated with Pearson's coefficient.

Table 4. Responsiveness of MOI-RA and DAS28.

Index	Change from baseline to 6 months mean (95% CI)	Change from baseline to 6 months %	SRM* (95% CI)	ES* (95% CI)
DAS28	-2.78 (-2.88 to 2.57)	50	2.0 (1.8 to 2.3)	2.8 (2.5 to 3.2)
MOI-RA28	-25.2 (-27.3 to -23.1)	65	1.8 (1.6 to 2.1)	1.9 (1.6 to 2.1)
MOI-RA42	-25.4 (-27.4 to -23.4)	65	1.8 (1.7 to 2.1)	1.9 (1.7 to 2.1)
MOI-RA 66/68	-23.1 (-25.0 to -21.2)	64	1.8 (1.6 to 2.1)	1.8 (1.6 to 2.0)

SRM: standardized response mean; ES: effect size. \* Confidence interval obtained by bias corrected bootstrapping (5000 replications).

significantly the outcomes between the 2 treatment arms of the FIN-RACo study.

MOI-RA results were similar regardless of which joint count (28, 42, and 66/68) was used. In other indices, joint counts are fixed. In DAS28<sup>10</sup> and SDAI<sup>13</sup>, 28 joint counts are used, and in the DAS, a 44-joint count is needed<sup>9,13</sup>. In

DAS, tender joint count is replaced with the Ritchie articular index<sup>38</sup>.

In large clinical RA studies, hard work is done to collect data from patients. It is not rare that some data are missing. If, for example, values of some patients' general health are missing, DAS28 cannot be calculated and those patients

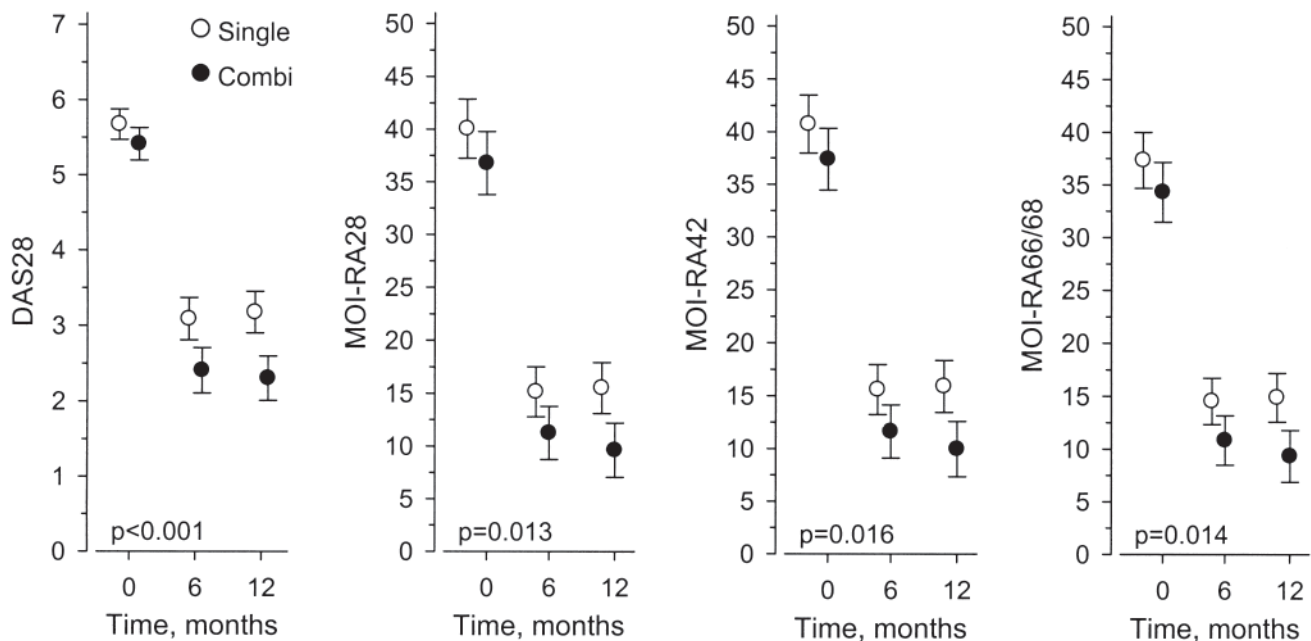


Figure 2. Decrease in DAS28 and MOI-RA in the monotherapy (Single) and combination therapy (Combi) arm of the FIN-RACo trial from baseline to 12 mos.

have to be omitted from the analyses. The high imputation stability of MOI-RA provides an opportunity to include in analyses patients with incomplete data.

A limitation of our study was that repeatability of MOI-RA was not studied. However, repeatability of the 7 components of MOI-RA has been studied on several occasions, since they all are components of ACR core set criteria and 4 of them included in DAS28, both widely accepted in RA assessment.

ACR-N<sup>15,24</sup> is a continuous index also based on the core set of ACR response criteria. ACR-N reports the lowest of the 3 values: percentage change in the number of tender joints, percentage change in the number of swollen joints, and median percentage change in the other 5 core set measures. Worsening of patients is represented in negative values. In accordance with the ACR response criteria, ACR-N cannot be used in cross-sectional studies. ACR-N may also be difficult to calculate in a busy clinical setting.

The MOI-RA index was designed for simplicity and feasibility, while incorporating patient physical function (HAQ). Calculation of MOI-RA might be more understandable for an ordinary rheumatologist with limited statistical education than calculation of DAS28. The components of MOI-RA include all the important measures of disease activity from both the physicians' and patients' perspectives. Further, MOI-RA has advantages compared to previous indices: various joint counts can be used with comparable outcome, and the imputation stability is high, enabling the use of incomplete data. The MOI-RA index merits additional testing in other patient populations.

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