The Disease Activity Score (DAS) and the Disease Activity Score using 28 joint counts (DAS28) in the management of rheumatoid arthritis

P.L.C.M. van Riel[1,2], L. Renskers[1]

[1]*Scientific Institute for Quality of Healthcare, Radboud University Medical Center, Nijmegen;*
[2]*Department of Rheumatology, Bernhoven, Uden, The Netherlands.*

Piet L.C.M. van Riel, MD, PhD
Lisanne Renskers, MSc

Please address correspondence to:
Piet L.C.M. van Riel,
Scientific Institute for Quality of Healthcare,
Radboud University Medical Center,
6500 Nijmegen, The Netherlands.
E-mail: piet.vanriel@radboudumc.nl

Received and accepted on September 20, 2016.

Clin Exp Rheumatol 2016; 34 (Suppl. 101): S40-S44.

Key words: DAS, DAS28, rheumatoid arthritis, personalised medicine, self-monitoring

Competing interests: none declared.

ABSTRACT

In rheumatoid arthritis (RA), disease activity cannot be measured in all individual patients according to a single variable.

The Disease Activity Score (DAS) and the DAS28 have been developed to measure disease activity in RA both in daily clinical practice as well as in clinical trials on a group as well as individual level. The DAS/DAS28 is a continuous measure of RA disease activity that combines information from swollen joints, tender joints, acute phase response and general health. The DAS-based EULAR response criteria were primarily developed to be used in clinical trials. The EULAR response criteria classify individual patients as non-, moderate, or good responders, dependent on the magnitude of change and level of disease activity reached. In addition, already in the early nineties, cut points were developed to categorise patients in remission. The DAS28 is incorporated in several electronic patient records and web-based systems for monitoring purposes in daily clinical practice. In addition to this, it is being used in combination with patient-reported outcome measures (PROMs) to facilitate self-monitoring.

Introduction

Rheumatoid arthritis (RA) is a chronic systematic inflammatory disease with peripheral synovitis as its main manifestation. The presentation of the disease and the course over time is highly variable both within as well as between individuals. The symptoms and signs of RA may vary from joint complaints like pain, stiffness, swelling and functional impairment, to more constitutional complaints like fatigue and loss of general health. Because of this variety in disease expression a huge number of variables have been used in the past decades to evaluate status and course of RA disease activity and its consequences (1).

Development of the DAS and DAS28

In clinical practice, often a judgement about the amount of disease activity is formed from a combination of information, such as laboratory and clinical variables, and overall impression of the patient (2). Formalising this clinical judgement to a quantifiable disease activity index would give an opportunity to compare the efficacy of treatments in different studies and improve the outcome by using such a score in the management of RA in daily clinical practice.

The DAS was developed using a large prospective study in which patients with an early RA were frequently assessed using many quantitative measures of disease activity. The decisions of rheumatologists to start a DMARD or to stop such treatment because of disease remission were taken as the gold standard for high disease activity and low disease activity, respectively (2, 3). With extensive statistical methods like discriminant factors and regression analysis, the Disease Activity Score (DAS) was developed. The DAS includes 2 comprehensive joint counts, the Ritchie Articular Index (RAI) and a 44 swollen joint count, plus the erythrocyte sedimentation rate and a general health assessment (VAS). As a VAS General Health is not always a available, a DAS using three variables was developed as well.

It was shown by Fuchs and Pincus that joint counts consisting of 28 joints are as valid and reliable as more comprehensive joint counts (4). Therefore, a modified disease activity score was developed, using 28 joint counts (5).

Table I. Different DAS-scores and formula for calculating these scores.

Score	Formula
Disease activity score (four variables) = DAS4	DAS4 = 0.53938*√(Ritchie) + 0.06465*(swollen joints) + 0.330*ln(ESR) + 0.00722* (general health)
Disease activity score (three variables) = DAS3	DAS3 = 0.53938*√(Ritchie) + 0.06465*(swollen joints) + 0.330*ln(ESR) + 0.224
Modified Disease Activity Score (four variables) = DAS28-4	DAS28-4 = 0.56*√(TJC28) + 0.28*√(SJC28) + 0.70*ln(ESR) + 0.014*(general health)
Modified Disease Activity Score (three variables) = DAS28-3	DAS28-3=[0.56*√(TJC28) + 0.28*√(SJC28) + 0.70*ln(ESR)]1.08 + 0.16

Validation of the DAS

The DAS was extensively validated against single variables and other indices used to measure disease activity in RA (2, 6, 7). In long term studies with 9 years follow-up the relationship between disease activity measured with the DAS, joint destruction and functional capacity was shown. In early RA, functional capacity was most associated with disease activity, and in late disease with joint damage (8). The specific influence of disease activity on progression of joint damage was also studied using the 9 year follow-up data using mixed models for longitudinal data for the analysis (9). It indicated that patients who had a constant low disease activity over time had about half the progression of joint damage as patients who had constant high disease activity (Fig. 1). Moreover, fluctuating disease activity added to progression of joint damage.

EULAR response criteria and remission criteria

Efficacy of treatment has generally been determined by comparing group means of changes in disease activity variables. However, a significant difference between groups does not readily indicate the actual number of patients who responded to treatment, which is of the utmost importance in the management of patients in daily clinical practice. In addition, individual response criteria may predict persistence of response or even remission, and appear more robust than response criteria solely based on percentage improvement such as ACR 20/50/70 (10). In cancer treatment for instance, tumour shrinkage is often labelled as response. However, tumour shrinkage (a relative measure) is not prognostic for survival in cancer, but a tumour below detection limit (an absolute measure) is. Therefore, response might incorporate an absolute level of disease activity similarly in RA, to provide optimal prognostic information. For these reasons, it was decided that response criteria should incorporate some significant amount of change as well as a certain level of low disease activity.

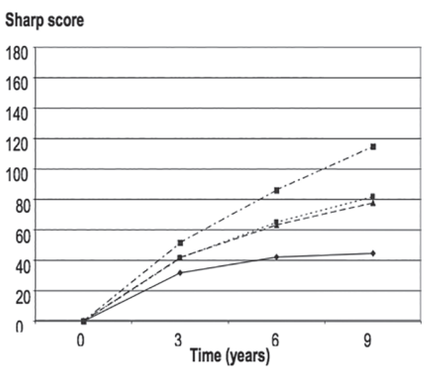

Fig. 1. Progression of joint damage is dependent of having a constant low DAS (lower curve), a constant high DAS (middle square curve), or a fluctuating high DAS (upper curve).

Table II. The EULAR response criteria using the DAS28.

Current DAS28:	Reduction of DAS28:		
	>1.2	>0.6 and ≤1.2	≤0.6
DAS28 ≤3.2	good	moderate	none
3.2 < DAS28 ≤5.1	moderate	moderate	none
DAS28 >5.1	moderate	none	none

Validity of EULAR response

The resulting EULAR response criteria based on DAS and DAS28 were extensively validated and compared with the ACR improvement criteria in several randomised trials (11, 12). It was concluded that ACR and EULAR definitions of response in RA performed similarly in differentiating active or experimental treatment from placebo or control treatment. In addition, the ACR and EULAR definitions of response performed comparably in association with overall assessments of improvement and progression of joint damage

The ultimate goal of medical treatment in RA may be formulated as to reach a state of remission (absence of disease activity), which may be temporarily and require ongoing therapy with DMARDs or "biological" agents. Finally, the patients should meet the recent proposed criteria of "Health" as having the ability to adapt and selfmanage (13). Although progress has been made in recent years to find a uniformly acceptable definition, there remain many definitions of remission in RA. Remission can be assessed clinically with the ACR/EULAR 2011 remission criteria using either the Boolean definition or an index based definition with the SDAI, which are very strict or by using the less stringent cut point of the Disease Activity Score (DAS or DAS28) (14, 15).

A DAS<1.6 or a DAS28<2.6 (Fig. 2) corresponds with being in remission according to the ARA criteria (16, 17). However, disease activity may not be regarded as an "on/off" phenomenon, and disease activity of a patient may fluctuate on a level of "no or minimal" disease activity. Accordingly, it may be preferable to express disease status of a patient as the cumulative amount of disease activity over a certain period of time or the mean disease activity in a certain period, rather than classifying a patient as in remission (18).

In daily clinical practice, visualising the course of the disease over time with the respective cut points for low disease ac-

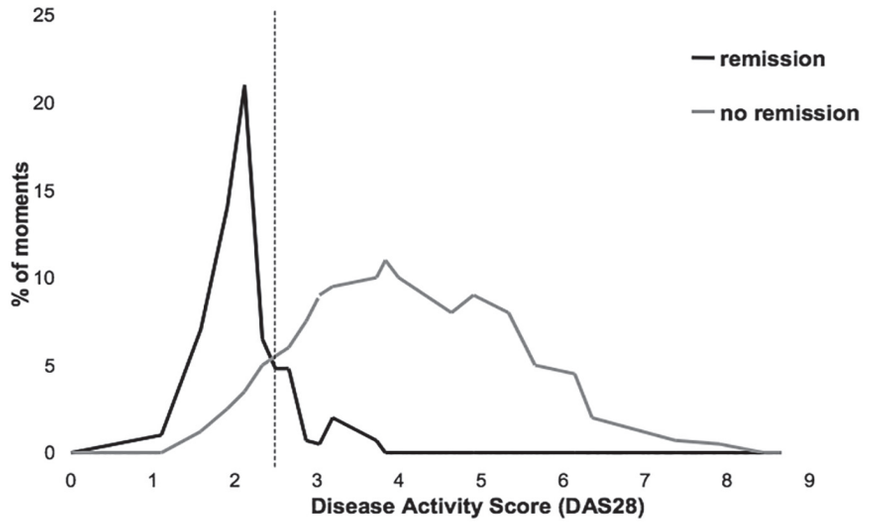

Fig. 2. A cut-off point of DAS28 <2.6 is associated with being in remission according to the ARA criteria.

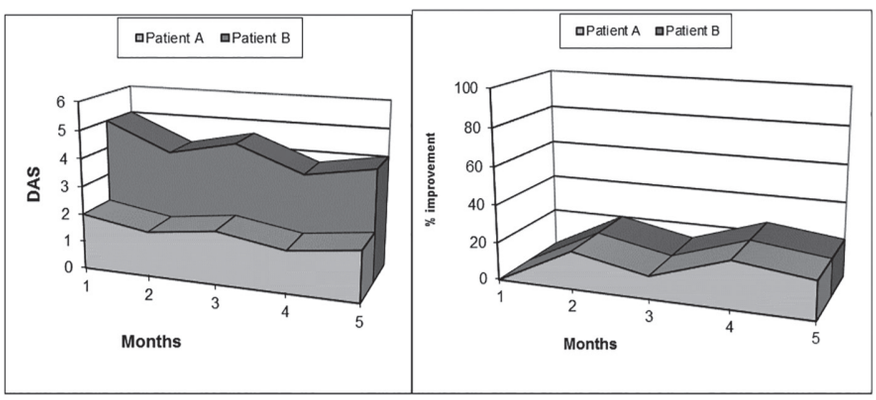

Fig. 3. Both fictitious patients A and B show equal (20%) improvement, but have highly different levels of disease activity. Van Riel PLCM, Van Gestel AM: *Arthritis Rheum* 2001; 44: 1719-22.

tivity and remission might be very useful. In addition, remission may not be the appropriate target in every patient, as has been shown that the influence of disease activity on joint damage is depending on baseline factors like ACPA positivity, erosiveness and acute phase response (19).

In addition, other factors, like for instance non-inflammatory musculoskeletal pain, depression or rheumatologist under-treatment, do play a role whether adjustment of therapy is undertaken in case of moderate to high disease activity (20).

Use in daily clinical practice

For clinical practice, there is general agreement that RA inflammation should be controlled as soon as possible, as complete as possible, and that control should be maintained for as long as possible, consistent with patient safety (21).

Accepting that the goal of treatment is to reach optimal control of RA inflammation or even remission, it is clear that management of RA should include systematic and regular evaluation of inflammation (22). Monitoring of long-term effects, especially disability and joint damage, may also be useful in practice. For assessment of rheumatoid inflammation in daily clinical practice, it is an advantage that the DAS and DAS28 are measures that are used in clinical studies, especially clinical trials. This facilitates knowledge transfer, or "evidence based practice", because it is easier to translate study results to the own practice. Further, as the DAS and DAS28 are absolute measures, they are suited to determine and evaluate the status and course of disease activity in individual RA patients. As noted earlier, relative measures, as the ACR improvement criteria, are not optimal for this purpose (Fig. 3) (23).

In practice, the DAS28 may appear to be more feasible than the DAS because of the reduced joint counts. At the same time, it must be clear that the DAS and DAS28 can support clinical decision-making, but do not replace careful patient history and physical examination. For instance, further investigations may be performed in case of discrepancies between the acute phase response and the joint scores. Infections or a "Fibromyalgia-like" behaviour can cause discrepant elevations in the acute phase response or tender joint count respectively.

In daily clinical practice, regular and systematic monitoring of inflammatory activity has several practical uses (24, 25).

The most important practical uses may be:

- Understand if the therapy chosen is needed and effective.
- Assure that rheumatoid inflammation is still under control
- Monitor to avoid over treatment
- Identify rapidly advancing disease, where "aggressive" treatment may be needed.
- Support the choice of specific DMARDs.
- Adjust DMARD dosage in the titration of disease activity.
- Support treatment expectations; *e.g.* a full response may take longer than expected, and it may be appropriate to continue the therapy if an adequate response may be achieved by additional treatment time.

An example of a programme used to systematically monitor disease activity in patients with RA is 'MijnReumacentrum' (26). This web-based database is both accessible by patients and healthcare providers, and provides among others information regarding the DAS28-score. All information relevant for determination of the DAS28-score is presented (tender joint counts swollen joint counts, ESR and VAS general health). Furthermore, details about the medication, quality of life (physical and psychological data) and various Visual Analogue Scales are presented (Fig. 4).

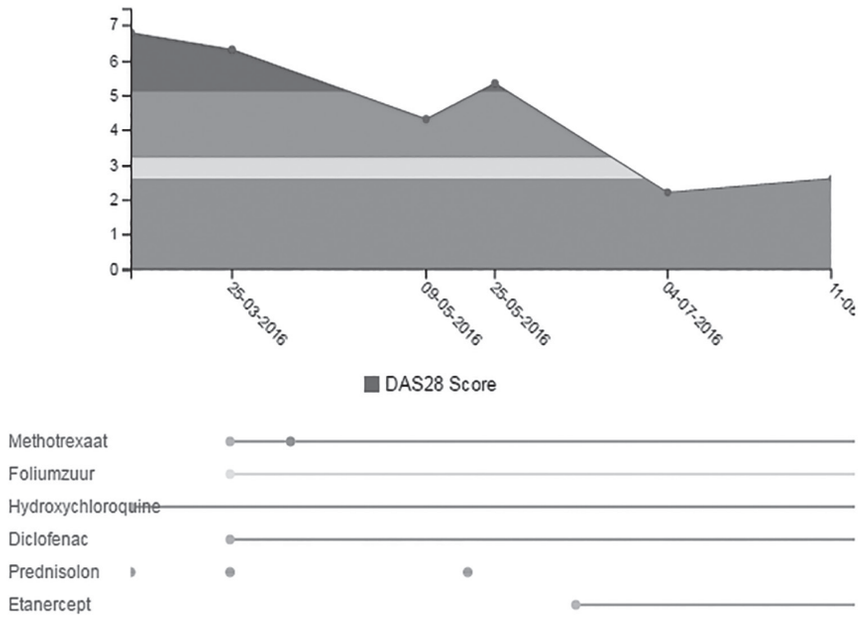

Fig. 4. Example of a patient using MijnReumacentrum.

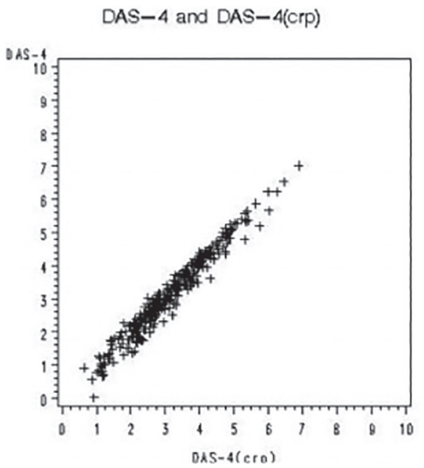

Fig. 5. Scatterplot of the DAS calculated using ESR (y-axis) and CRP (x-axis).
DAS formulas using CRP:
DAS28-CRP=0.56*(TJC28)+0.28*√(SJC28)+ 0.36*ln(CRP+1)+ 0.014*(General Health) + 0.96.
DAS-CRP=0.54*√(RAI)+0.065(SJC44)+ 0.17*ln(CRP+1)+0.0072*(General Health)+ 0.45.

Using CRP or ESR?

C-reactive protein (CRP) may be used as an alternative to ESR in the calculation of the DAS or DAS28 (27). CRP is a more direct measure of inflammation than ESR, and it has a more rapid increase after an inflammatory stimulus (28). CRP production, like ESR, is associated with radiological progression in RA, and is considered at least as valid as ESR to measure RA disease activity. Prospectively collected data from the Nijmegen University Hospital cohort of RA patients (n=334) were used for development and testing (split-sample). As ESR and CRP are not identical, the relationship between transformations of ESR and CRP was imperfect, especially in the lower ranges. But the relationship was linear and did not change over time. New DAS and DAS28 formulas including CRP were devised using linear regression, with the purpose to give a good estimate of DAS values on group level (Fig. 5). However, there was a considerable lack of individual agreement, therefore DAS28-ESR and DAS28-CRP scores are not interchangeable within individuals. In general, the DAS28-CRP scores are around 0.2 points lower than the DAS28-ESR scores (29).

Self monitoring using an online tool

Several online tools have been developed to encourage patients to take an active role in their disease management and to enhance the dialogue between healthcare providers and patients. An example is iMonitor which was developed and made accessible by personal computer, laptop, tablet or smartphone (30). The main feature of iMonitor is the collection of Patient Reported Outcome Measures (PROMs). These PROMs can be filled in by patients at any time, with a maximum amount of one per day. The programme meets privacy standards and is only accessible by a PIN code and data is protected during storage.

Since the disease activity of patients with RA tends to fluctuate between visits (31, 32), close monitoring is required, particularly as fluctuations in disease activity are directly related to changes in radiologic progression (9) (Fig. 1). Patients are able to fill in a PROM at any desired moment, however, reminder emails can be send at fixed time points (for example weekly or monthly), determined by the patient and the health professional. After filling in a PROM/PROMs, a graph appears with the scores (Fig. 6). Moreover, when a DAS28 score is available for a patient, this score can be placed next to the PROM-score(s) in the graph by a healthcare professional. This allows the patient as well as the professional to have an insight in the course of the disease by means of a graph with subjective measures (PROM-scores), as well as objective measures (DAS28-scores).

Another advantage of iMonitor is the integrated alert system. In case the disease activity exceeds a predetermined threshold, iMonitor sends an alert to the physician. This enables identification of patients whose disease activity is not in line with the target. Patients who need further medical attention can be identified and they could receive additional medical attention between visits. Furthermore, completion of a PROM helps the patient to prepare for their visit and it could improve the communication between physician and patient as well as the adherence to the treatment (33).

PROMs used in iMonitor are the Health Assessment Questionnaire (HAQ), the Patient derived Disease Activity Score 28 joint count (PtDAS28), the Rheumatoid Arthritis Disease Activity Index-5 (RADAI-5) and the Rheumatoid Arthritis Impact of Disease (RAID). These PROMs have shown to correlate well with objectively assessed measures and have good psychometric properties. Furthermore, they bring additional information about other domains (for example functional status and impact of disease) beyond joint counts or acute phase reactants (34).

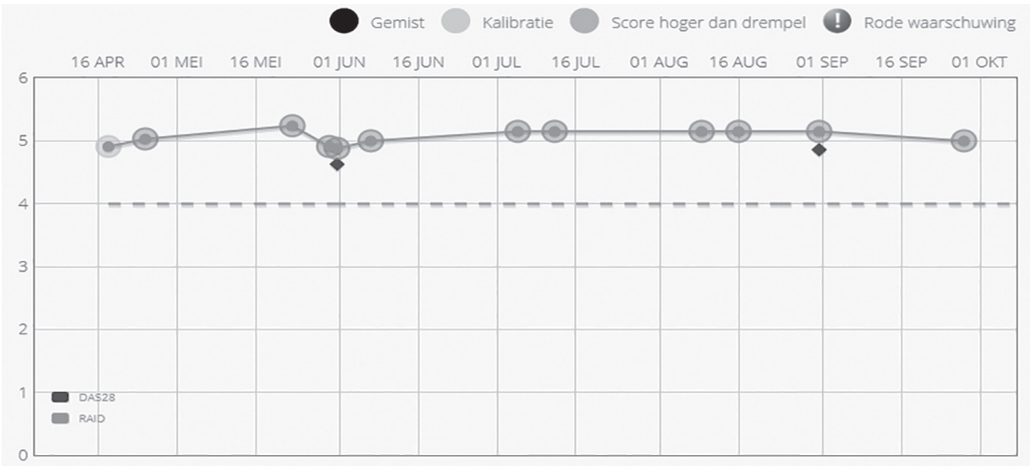

Fig. 6. Example of a graph representing PROM-scores of a patient.
Red bullets: score higher than threshold.
Grey bullets: calibration period.
Black bullet: missing report.

References

1. VAN RIEL PLCM, VAN DE PUTTE LBA: Clinical assessment and clinical trials in rheumatoid arthritis. *Curr Opin Rheumatol* 1994; 6: 132-9.
2. VAN DE HEIJDE DMFM, VAN'T HOF MA, VAN RIEL PLCM, VAN DE PUTTE LBA: Validity of single variables and indices to measure disease activity in Rheumatoid Arthritis. *J Rheumatol* 1993; 20: 538-41.
3. VAN DE HEIJDE DMFM, VAN'T HOF MA, VAN RIEL PLCM *et al*.: Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. *Ann Rheum Dis* 1990; 49: 916-20.
4. FUCHS HA, BROOKS RH, CALLAHAN LF, PINCUS T: A simplified twenty-eight-joint quantitative articular index in rheumatoid arthritis. *Arthritis Rheum* 1989; 32: 531-7.
5. PREVOO MLL, VAN'T HOF MA, KUPER HH, VAN LEEUWEN MA, VAN DE PUTTE LBA, VAN RIEL PLCM: Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with Rheumatoid Arthritis. *Arthritis Rheum* 1995; 38: 44-48.
6. VAN DER HEIJDE DMFM, VAN'T HOF MA, VAN RIEL PLCM, VAN LEEUWEN MA, VAN RIJSWIJK MH, VAN DE PUTTE LBA: Validity of single variables and composite indices for measuring disease activity in rheumatoid arthritis. *Ann Rheum Dis* 1992; 51: 177-81.
7. VAN DER HEIJDE DMFM, VAN RIEL PLCM, VAN LEEUWEN MA, VAN'T HOF MA, VAN RIJSWIJK MH, VAN DE PUTTE LBA: Prognostic factors for radiographic damage and physical disability in early rheumatoid arthritis. A prospective follow-up study of 147 patients. *Br J Rheumatol* 1992; 31: 519-25.
8. WELSING PMJ, VAN GESTEL AM, SWINKELS HL, KIEMENEY LALM, VAN RIEL PLCM: The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. *Arthritis Rheum* 2001; 44: 2009-17.
9. WELSING PMJ, LANDEWÉ RB, VAN RIEL PLCM *et al*.: The relationship between disease activity and radiological progression in patients with rheumatoid arthritis: a longitudinal analysis. *Arthritis Rheum* 2004; 50: 2082-93.
10. FELSON DT, ANDERSON JJ, BOERS M *et al*.: American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 727-35
11. VAN GESTEL AM, HAAGSMA CJ, VAN RIEL PLCM: Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. *Arthritis Rheum* 1998; 41: 1845-50
12. VAN GESTEL AM, ANDERSON JJ, VAN RIEL PLCM *et al*.: ACR and EULAR improvement criteria have comparable validity in rheumatoid arthritis trials. *J Rheumatol* 1999; 26: 705-11.
13. HUBER M, KNOTTNERUS JA, GREEN L *et al*.: How should we define health? *BMJ* 2011; 343: d4163.
14. FELSON DT, SMOLEN JS, WELLS G *et al*.: American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis Rheum* 2011; 63: 573-86.
15. PUNDER YMR, FRANSEN J, KIEVIT W *et al*.: The prevalence of clinical remission in RA patients treated with anti-TNF: results from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry. *Rheumatology* 2012; 51: 1610-7.
16. PREVOO MLL, VAN GESTEL AM, VAN'T HOF MA, VAN RIJSWIJK MH, VAN DE PUTTE LBA, VAN RIEL PLCM: Remission in a prospective study of patients with rheumatoid arthritis. *Br J Rheumatol* 1996; 35: 1101-5.
17. FRANSEN J, WELSING PMJ, VAN RIEL PLCM: Remission in RA: Agreement of the Disease Activity Score (DAS28) with the ARA preliminary remission criteria. *Ann Rheum Dis* 2003; 62 (Suppl. 1): 68.
18. VAN RIEL PLCM, VAN GESTEL AM: Clinical outcome measures in rheumatoid arthritis. *Ann Rheum Dis* 2000; 59 (Suppl. I): i28-i31.
19. DE PUNDER YMR, JANSEN TLTHA, VAN EDE AE, DEN BROEDER AA, VAN RIEL PLCM, FRANSEN J: Personalizing treatment targets in rheumatoid arthritis by using a simple prediction model. *J Rheumatol* 2015; 42: 398-404.
20. TYMMS K, ZOCHLING J, SCOTT J *et al*.: Barriers to optimal disease control for rheumatoid arthritis patients with moderate and high disease activity. *Arthritis Care Res* 2014; 66: 190-6.
21. MORELAND LW, RUSSELL AS, PAULUS HE: Management of rheumatoid arthritis: the historical context. *J Rheumatol* 2001; 28: 1431-52.
22. VAN RIEL PLCM, SCHUMACHER HR: How does one assess early rheumatoid arthritis in daily clinical practice? *Best Pract Res Clin Rheumatol* 2001; 15: 67-76.
23. VAN RIEL PLCM, VAN GESTEL AM: Area under the curve for the American College of Rheumatology improvement criteria: a valid addition to existing criteria in rheumatoid arthritis? *Arthritis Rheum* 2001; 44: 1719-22.
24. FRANSEN J, STUCKI G, VAN RIEL PLCM: The merits of monitoring: should we follow all our rheumatoid arthritis patients in daily practice? *Rheumatology* 2002; 41: 601-4.
25. WOLFE F, CUSH JJ, O'DELL JR *et al*.: Consensus recommendations for the assessment and treatment of rheumatoid arthritis. *J Rheumatol* 2001; 28: 1413-30.
26. Transparency in Healthcare B.V. (TiH) (2016) Available from: http://www.tihealthcare.nl/en.
27. FRANSEN J, WELSING PMJ, DE KEIJZER RMH, VAN RIEL PLCM: Development and validation of the DAS28 using CRP. *Ann Rheum Dis* 2003; 62 (Suppl. 1): 10.
28. VAN LEEUWEN MA, VAN RIJSWIJK MH: Acute phase proteins in the monitoring of inflammatory disorders. *Bailliere's Clin Rheumatol* 1994; 8: 531-52.
29. VAN RIEL PLCM, FRANSEN J, SCOTT DL: EULAR handbook of clinical assessments in rheumatoid arthritis. Alphen aan den Rijn: van Zuiden Communications 2004.
30. MEDICAL AND EDUCATIONAL GOODS AND SERVICES (MEGS): iMonitor (2016). Available from: http://www.pfizer.co.uk/content/medical-and-educational-goods-and-services-megs-imonitor.
31. BERTHELOT J, BLANCHAIS A, MARHADOUR T, LE GOFF B, MAUGARS Y, SARAUX A: Fluctuations in disease activity scores for inflammatory joint disease in clinical practice: do we need a solution? *Joint Bone Spine* 2009; 76: 126-8.
32. BERTHELOT JM, TORTELLIER L, LAVY-BREGEON D, LE GOFF B, MAUGARS Y: High intraindividual week-to-week variability in BASDAI and BASFI values: Are several evaluations needed before starting or stopping TNF-α antagonist therapy for spondyloarthropathies? *Joint Bone Spine* 2008; 75: 167-71.
33. EL MIEDANY Y: PROMs in inflammatory arthritis: moving from static to dynamic. *Clin Rheumatol* 2013; 32: 735-42.
34. GOSSEC L, DOUGADOS M, DIXON W: Patient-reported outcomes as end points in clinical trials in rheumatoid arthritis. *RMD Open* 2015; 1: p. e000019.