THE EFFECTIVENESS OF SYSTEMATIC MONITORING OF RA DISEASE ACTIVITY IN DAILY PRACTICE (TRAC): A MULTI CENTRE, CLUSTER-RANDOMISED CONTROLLED TRIAL.

- Extended report

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Abstract

**Objective:** The objective of this 24-week cluster-randomised trial was to test the efficacy of standardised monitoring using the DAS28, versus usual care, on DMARD prescription and disease activity in RA.

**Methods:** Rheumatology out-centres were randomised to systematic monitoring of disease activity using the DAS28 (12 centres, 205 RA patients) or usual care (12 centres, 179 RA patients). The aim for the DAS group was to reach a DAS28 $\leq 3.2$ by changes in DMARD therapy, at the discretion of rheumatologist and patient.

**Results:** At baseline, disease activity was the same in both groups, with an overall mean (SD) DAS28 of 4.5 (1.2) and overall 13% of the patients had a DAS28 $\leq 3.2$. At 24 weeks, 31% of patients in the DAS group had a DAS28 $\leq 3.2$, whereas in the usual care centres this was 16% (p=0.028). DMARDs were changed on average in 18% of visits in the DAS centres; in the 12 usual care centres this was 8% (p=0.013). The doses of MTX, SASP and corticosteroids appeared to be higher in the DAS centres than in the usual care centres, but these differences were not significant.

**Conclusion:** In daily practice, systematic monitoring of disease activity in RA may lead to more changes in DMARD therapy, resulting in more patients with low disease activity.
Introduction
For the management of RA, there is general agreement that rheumatoid inflammation should be controlled as soon as possible, as completely as possible and for as long as possible, consistent with patient safety [1,2]. When the goal of RA treatment is to reach optimal control of rheumatoid inflammation, it is clear that rheumatoid inflammation should systematically be evaluated. Subsequently, the treatment program can be adjusted from both perspectives of benefit and harm [3]. The combination of systematic evaluation and clinical guidelines could provide valuable decision support in optimising the management of RA. The effects of such decision support should preferably be studied using a randomised, controlled trial design (RCT) [4]. However, when studying the effects of decision support (such as guidelines) in a trial, it is generally not necessary to study the effect on health [5]. Because, if included guidelines are based on sound evidence, it is already known that the targeted behaviour will be beneficial. For example, the ‘efficacy’ of guidelines to improve folate supplementation in addition to MTX can be evaluated by simply counting the number of correct prescriptions. However, in the case of guidelines for the control of rheumatoid inflammation in RA, physician performance as reflected by DMARD prescription is more difficult to judge: prescribing more DMARDs is not identical to better therapy. Therefore, the proportion of patients with adequately controlled rheumatoid inflammation (e.g. DAS28 ≤ 3.2) can be proposed as a proxy for physician performance in such trials [4]. Having a low level of rheumatoid inflammation (DAS28 ≤ 3.2) over time is associated with up to 50% less progression of joint damage [6]. Also, functional capacity (HAQ) is predominantly determined by rheumatoid inflammation (DAS) early in the disease, and by joint damage later [7]. The advantages to using the DAS28 [8,9] for the assessment of rheumatoid inflammation in daily practice are: 1) The DAS28 is more valid to measure underlying rheumatoid inflammation than individual variables of rheumatoid inflammation. 2) The continuous scale of the DAS28 has absolute meaning, making its value interpretable, unlike a measure of % change. 3) Low disease activity according to DAS28 ≤ 3.2 reflects a clinical meaningful target for DMARD treatment. 4) The DAS is also used in clinical trials, which makes it easier to translate trial results into clinical practice. The objective of this trial was to test the efficacy of standardised monitoring using the DAS28, versus usual care, on DMARD prescription and disease activity in RA.
Methods
This study was a multi-centre, 24-week, cluster-randomised controlled trial of systematic monitoring using the DAS28 (DAS group) versus usual care (UC group) in RA. In addition, all included patients started using Celecoxib 200 mg 2dd, a COX-2 specific inhibitor. The results of the Celecoxib use will be reported separately. The primary endpoints of this study were 1) the proportion of patients reaching low disease activity (DAS28 ≤ 3.2) at week 24, in a subgroup of patients; 2) the changes in DMARD therapy during 24 weeks, in all patients. Secondary endpoints were: 1) the dose changes in individual DMARDS, and 2) changes in patient-assessed pain, global disease activity and disability.

To determine the proportion of patients with a DAS28 ≤ 3.2 in this trial, the DAS28 had to be independently assessed. For reasons of efficiency, these independent assessments only took place in a subgroup of patients, consisting of all patients from the participating centres in a predetermined geographical region.

Sample
24 rheumatology out-centres throughout the Netherlands were willing to participate in the study. A statistician used a random number generator to randomly allocate the centres to DAS (12 centres) or UC (12 centres). All patients within a centre were treated the same way. Randomisation took place in 2 strata: one stratum consisted of the participating centres in the predetermined region, the other stratum consisted of all other participating centres. Centre allocation remained concealed until the start of patient recruitment. The period of recruitment started in March 2000 and ended in March 2001. Patients with RA who were in need of NSAID treatment were asked to participate by their treating rheumatologist. All included patients started treatment with Celecoxib 200 mg 2dd.

Inclusion criteria were: out-patients of at least 18 years of age with RA according to the ACR criteria; medical need for NSAID treatment; adequate anticonception; provision of informed consent.

Exclusion criteria were: History of allergy for NSAIDs; serious bowel, liver, kidney or heart disease; coagulopathy; (suspicion of) peptic ulcer or gastro-intestinal bleeding; malignancy; substance abuse or mental disorders that interfere with study participation.

Interventions
In the DAS group, systematic monitoring of disease activity was performed at week 0, 4, 12 and 24, by assessment of the DAS28 by the treating rheumatologist. According to the study guidelines, the aim was to reach a DAS28 ≤ 3.2 (low disease activity) by changing DMARD therapy if the DAS28 was higher than 3.2 [9]. The rheumatologists of the DAS group had been instructed in performing the joint counts and in using a special calculator for the DAS28.

In the UC group, no systematic monitoring of disease activity was done and no guideline to adapt treatment strategy was supplied. Otherwise, the study visits were identical in both groups.

Assessments
Registration of past and current medication use took place at 0, 4, 12 and 24 weeks. A stop, start, addition of a DMARD or a change in DMARD dose was considered to be a change in DMARD therapy.
The DAS28 was calculated according to the formula by Prevoo et al. [8]. The DAS28 includes a 28 tender joint count, a 28 swollen joint count, ESR and a general health item (GH). ESR was determined locally using the Westergren method. GH was rated by the patient on a numerical rating scale of 0 (very well) to 10 (very bad), which was rescaled to range from 0-100.

Patient assessed pain and global disease activity were also rated on numerical rating scales from 0-10. A validated Dutch version of the disability index of the Stanford Health Assessment Questionnaire (HAQ) was used to assess disability, the HAQ ranges from 0-3 [10].

In addition, the joint counts for the DAS28 were independently assessed at weeks 0 and 24, in the 3 DAS and 4 UC centres, which were in the predetermined geographical region. Specially trained research nurses performed these joint counts. The rheumatologists did not have access to the results of these assessments.

Statistical analysis
The data were analysed using linear regression with random coefficients (mixed models), correcting for clustering of the data in centres (all analyses) and additionally correcting for repeated measurements (analysis of DMARD changes). An intention-to-treat approach with last observation carried forward was used for the analysis of primary outcomes. P-values < 0.05 were considered statistically significant.

In addition, the agreement between the DAS28 as assessed by the rheumatologists and the independent research nurses was analysed using an intra class correlation coefficient (ICC2,1) for agreement. The analyses were performed using the SAS 8.0 statistical software package.

Sample size determination
The sample size needed was calculated for detecting differences in disease activity in the subgroup. The expected mean (SD) change in DAS28 in the DAS group was -1.0 (1.0) and in the UC group -0.5 (1.0). With $\alpha=0.05$ and $1-\beta=0.90$ it would need $2 \times 85 = 170$ patients. Then, a 16% difference in the proportion of patients with DAS28 ≤ 3.2 would be significant if the mean (SD) DAS28 at baseline is 4.2 (1.2), which is a usual mean DAS28 for samples from the RA clinical population. It was expected that the degree of clustering, and therefore inflation of sample size, would be low (ICC=0.005) because of the independent assessment of the DAS28.
Results

Sample

The 12 centres in the DAS group enrolled 205 patients, and the 12 UC centres
enrolled 179 patients. Patients of both groups were comparable at baseline (Table 1)
except for RF positivity (p<0.05 in main sample and subgroup). There were no other
statistically significant differences. In the DAS group there were 16/205 (8%)
dropouts, for the following reasons: adverse event (n=3); patient wish (n=5); other
reason (n=8). In the UC group there were 20/179 (11%) dropouts: adverse event
(n=9); patient wish (n=7); other reason (n=4). Dropouts for “other reason” included
protocol violations by starting Leflunomide (5 in DAS group and 2 in UC group) or
Infliximab (1 in DAS group).

Table 1. Baseline variables for the main study (N=384) and its subgroup (N=142).

<table>
<thead>
<tr>
<th></th>
<th>Main sample</th>
<th>Sub sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DAS n=205</td>
<td>Usual Care n=179</td>
</tr>
<tr>
<td>Female, n</td>
<td>138 (67%)</td>
<td>132 (74%)</td>
</tr>
<tr>
<td>Disease duration (yrs), median (IQR)</td>
<td>6 (3-14)</td>
<td>7 (3-14)</td>
</tr>
<tr>
<td>Age (yrs), mean (SD)</td>
<td>58 (52-65)</td>
<td>58 (50-70)</td>
</tr>
<tr>
<td>RF positive, n</td>
<td>172 (84%)</td>
<td>132 (74%)</td>
</tr>
<tr>
<td>Rheumatoid Nodules, n</td>
<td>43 (21%)</td>
<td>37 (21%)</td>
</tr>
<tr>
<td>Joint damage present, n</td>
<td>135 (65%)</td>
<td>108 (60%)</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>20 (10-32)</td>
<td>19 (10-35)</td>
</tr>
</tbody>
</table>

Disease activity

Reaching low disease activity was determined for the sub sample only (N=142). At
baseline, the DAS (n=61) and UC (n=81) groups had comparable levels of disease
activity. The mean (SD) DAS28 at baseline was 4.6 (1.2) in the DAS group and 4.5
(1.2) in the UC group (t-test, p=0.44), and 8/61 (13%) patients in the DAS group had
low disease activity (DAS28 ≤ 3.2) and 10/81 (12%) in the UC group (X², p=0.91).
At 24 weeks, the number of patients with low disease activity in the DAS group
increased to 19/61 (31%), whereas in the UC group there were 13/81 (16%) (Figure
1). The mean difference (95% CI) in proportion of patients with low disease activity at
week 24 was 15% (3%-27%), (mixed models; p=0.028). The mean (SD) changes in
DAS28 over 24 weeks were -0.40 (1.0) in the DAS group and -0.14 (1.2) in the UC
group (mixed models; p=0.36). The DAS28 values as assessed by the
rheumatologists and the independent research nurses agreed with ICC=0.88 at week
0, and ICC=0.89 at week 24.

DMARD changes

At baseline, Methotrexate (MTX) and Sulfasalazine (SSZ) were the DMARDs most
often used (Table 2). There were no statistically significant baseline differences
between both groups. In the DAS centres, there were more DMARD changes during
the study (Figure 2). DMARD changes took place on average in 20% of visits in the
DAS centres; in the UC centres this was 9%. The corrected mean difference (95% CI) was 9% (2%-16%), (mixed models; p=0.013).
Table 2. DMARD, Corticosteroid and NSAID use at study start. The percentages do not add up to 100, because of combination therapy. DMARDs used by single patients were summed up as “other DMARDs.”

<table>
<thead>
<tr>
<th>Medication</th>
<th>n=205</th>
<th>n=179</th>
<th>n=384</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>94 (46%)</td>
<td>93 (52%)</td>
<td>187 (49%)</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>54 (26%)</td>
<td>47 (26%)</td>
<td>101 (26%)</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>31 (15%)</td>
<td>17 (10%)</td>
<td>48 (13%)</td>
</tr>
<tr>
<td>Aurothioglucose</td>
<td>16 (8%)</td>
<td>8 (5%)</td>
<td>24 (6%)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>6 (3%)</td>
<td>3 (2%)</td>
<td>9 (2%)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>7 (3%)</td>
<td>1 (1%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Other DMARDs</td>
<td>3 (1%)</td>
<td>5 (3%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>44 (21%)</td>
<td>25 (14%)</td>
<td>69 (18%)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>172 (84%)</td>
<td>133 (74%)</td>
<td>305 (79%)</td>
</tr>
</tbody>
</table>

Medication use
To provide insight into the nature of changes in medication, the mean dose of the three most frequently used medications is shown in Figures 3 A-C. Seen graphically, it appeared that dosages were higher in the DAS group. However, there were no statistically significant differences between the DAS and UC groups in mean MTX dose (mixed models; p=0.11), mean SSZ dose (mixed models; p=0.27), and mean Prednisone dose (mixed models; p=0.29). There also appeared to be no large differences in the amount of non-oral steroids administered. Regarding Celecoxib use, a small number of patients continuing the study stopped using this drug. In the DAS group 21/205 (10%) stopped using Celecoxib (n=9 because of adverse events), and in the UC group 22/179 (12%) stopped its use (n=13 because of adverse events).

Patient assessments
At baseline, there were no significant differences in assessments of pain, global disease activity and disability between the patients of the DAS and UC groups. The improvements in patient assessments appeared to be larger in the DAS group than in the UC group, but there was a statistically significant difference in patient global assessment of disease activity only (not shown).

Adverse events
The most frequently occurring adverse events were: upper abdominal pain 50/384 (13%), infections 42/384 (11%), rash or itching 29/384 (8%), nausea or vomiting 24/384 (6%) and headaches 18/384 (5%). There were statistically significant differences (p<0.05) only for rash or itching (DAS group 4% and UC group 11%) and nausea or vomiting (DAS group 4% and UC group 9%). There appeared to be no tendency that adverse events occurred more often in the DAS group.

Adherence to the intervention
In the DAS group, the DAS28 was calculated by the rheumatologists in 99% of the visits, and 93% of the DMARD changes occurred when disease activity was moderate or high. However, in all those instances of DAS28>3.2, on average only in 20% a DMARD change took place. The most frequently mentioned reasons not to change DMARDs although the DAS28 was above 3.2, were: “wait and see” or “disease activity is assessed as sufficiently low” (Table 3).
### Table 3

<table>
<thead>
<tr>
<th>Reason not to change medication when DAS28 &gt; 3.2</th>
<th>n=</th>
</tr>
</thead>
<tbody>
<tr>
<td>Await effect of current medication (including Celebrex)</td>
<td>78 (84%)</td>
</tr>
<tr>
<td>RA activity is judged sufficiently low by rheumatologist</td>
<td>50 (54%)</td>
</tr>
<tr>
<td>Medication dose already maximal / adverse events</td>
<td>39 (42%)</td>
</tr>
<tr>
<td>Patient wish / patient is satisfied</td>
<td>29 (31%)</td>
</tr>
<tr>
<td>DAS28 is high for other reasons than disease activity</td>
<td>10 (9%)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>93 (100%)</td>
</tr>
</tbody>
</table>

Table 3. Reasons of rheumatologists *not* to change medication at visits where the DAS28 > 3.2, were mentioned in 93 of the DAS patients. Percentages do not add up to 100 because different reasons could be mentioned at different visits.
Discussion
This multi centre cluster-RCT of standardised monitoring of disease activity versus usual care showed that standardised monitoring resulted in 1) more changes in DMARD therapy during the 24-week study period, and 2) a twice larger proportion of patients with low disease activity at 24 weeks. It can be concluded that standardised monitoring of disease activity in RA with the aim to reach low disease activity improves the management of RA patients in daily clinical practice. There are several ways in which standardised monitoring is useful in clinical practice: monitoring can be used to measure and document treatment need, it can support the use of specific DMARDs, it can ensure that rheumatoid inflammation is still under control, it is useful to understand whether the therapy chosen is necessary and effective, and it can ensure that no over treatment is performed [2]. Apart from assessing disease activity, monitoring may include assessments for disability and joint damage [11]. At the same time, it must be clear that standardised measures can support clinical decision-making, but they do not replace careful patient examination and inquiry [11]. Experienced rheumatologists may make risk-benefit assessments and decisions about therapies (with their patients) that are hard to capture or standardize with standard measures.

In this study, we chose to add only the evaluation of rheumatoid inflammation to usual care, because rheumatoid inflammation is the primary target of DMARD therapy. Although we found a relevant and significant difference in the proportions of patients with low disease activity (DAS28 ≤ 3.2) at 24 weeks, the decrease in rheumatoid inflammation was smaller than expected, and was statistically significant in the difference in proportions of patients with DAS28 ≤ 3.2, but not in the difference in the continuous DAS28. The latter is unexpected, as usually power is lost when dichotomising a continuous measure, but it may be explained by the DAS28 ≤ 3.2 being a more direct reflection of the provided study guidelines. The reasons underlying the relatively small difference between DAS group and UC group are probably 1) the freedom of choice of treatment options within the study guidelines; and 2) starting a new medication (Celecoxib) at baseline. Both may have lead to less DMARD changes in the DAS group than might have been possible. Of note, in 80% of instances with a DAS28 > 3.2 in the DAS group, the DMARD therapy remained unchanged. The reasons not to change DMARDs given by the physicians indicated that often the level of inflammation reached was judged as satisfactory. However, at DAS28 levels larger than 3.2, rheumatoid inflammation is certainly not sufficiently controlled [6,9]. This discrepancy between satisfaction and objective level of rheumatoid inflammation may require more attention in future studies and implementation initiatives. To our experience, physicians and patients are often satisfied with treatment because of a certain decrease in inflammation. However, the goal of therapy is not so much to induce a decrease, but to keep inflammation under control, for which further adaptations in DMARD therapy may be necessary [2,3].

This trial was a cluster-randomised trial with the outcome being measured and analysed at patient level (as opposed to analysis at cluster level), correcting for the dependency of patients within clusters by using mixed models. Especially of concern in cluster randomised trials, the patient samples were comparable at baseline, particularly also on the primary outcome variables DAS28 and medication use. As the participating physicians could not be blinded, it was necessary to measure the DAS28 independently, but unfortunately this could not be performed in all centres. A larger sample would not necessarily have lead to finding different DAS28 changes, but to better precision in the estimation of differences. The number of dropouts in this
study was small and comparable in both study groups, and the results of the intention-to-treat analysis did not differ from the per protocol analysis. For all these reasons, we feel that it is unlikely that the results of this study can be explained by bias in its design.

Evidence regarding the effects of monitoring of disease activity in RA is scarce. Monitoring and guidelines are no interventions that will cause health effects in themselves, but medication may do so. This indirectness makes it difficult to study and detect "health effects" of monitoring and guidelines. There are 2 pre-experimental studies finding moderate evidence in favour of monitoring [12,13], and recently another RCT was published [14]. In that study, a combination of systematic monitoring of disease activity and a strict protocol of escalating DMARD therapy, versus usual care (UC), was investigated in patients with active and early RA. In 24 weeks the mean DAS28 (as converted from the original DAS [9]) of the UC group decreased from 5.8 to 4.6, but the DAS28 of the monitoring group decreased much more, from 6.2 to 3.4. A mean DAS28 of 3.4 means that between 40-50% of the patients will have low disease activity (DAS28 ≤ 3.2) according to the DAS28. To compare, in our study 31% had such a low DAS28 at 24 weeks. A major difference between both RCTs is that the intervention by Grigor et al. was performed by a single rheumatologist who used a strict protocol of escalating DMARD therapy with monthly visits, where in our study the choice of DMARD therapy was at the discretion of the treating rheumatologists and visits were less frequent. These studies provide evidence that in daily practice, systematic monitoring of disease activity in RA may lead to more changes in DMARD therapy, resulting in more patients with low disease activity. A more strict use of monitoring and guidelines in the targeting of DMARD therapy may probably lead to better results.
Acknowledgements
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Competing interests
None declared.

Ethical approval
The study protocol has been approved by ethics committee (CMO) of the University Medical Centre Nijmegen as well as by the ethics committees of all participating centres.

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**FIGURE LEGENDS**

**Figure 1.** In the DAS group, more patients reached low disease activity (DAS28 ≤ 3.2) than in the Usual Care group (p=0.028).

**Figure 2.** In the DAS group, more DMARD changes occurred during the course of the study (p=0.013).

**Figures 3A-C.** Mean dose of Methotrexate (MTX), Sulfasalazine (SSZ) and oral Prednisone during the course of the study.
Literature
The effectiveness of systematic monitoring of RA disease activity in daily practice (TRAC): a multi centre, cluster-randomised controlled trial
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