Previously we have reported on the development of the Compliance-Questionnaire-Rheumatology (CQR), a rheumatology-specific instrument that measures patient compliance to drug regimens, identifies factors that contribute to suboptimal patient compliance, and possibly can be used to predict future compliance in patients with rheumatoid arthritis (RA), polymyalgia rheumatica (PMR), and gout.

The 19-item instrument had encouraging psychometric properties: good test-retest reliability and moderate internal consistency, and validation using discriminant analyses showed a sensitivity of 98%, a specificity of 67%, and an estimated kappa of 0.78 to detect low compliance. We concluded that the CQR was well accepted, and that it was useful to detect possible barriers for optimal compliance and predicting patient compliance to a drug regimen, based on the comparison with the self-report of patient compliance as a surrogate gold standard.
were encouraging, the development procedure lacked a formal validation against a gold standard. An ideal compliance measurement instrument to validate the CQR against should be simultaneously unobtrusive (to avoid patient sensitization and maximize cooperation), objective (to produce discrete and reproducible data for each subject), and practical (to maximize portability and minimize cost)\textsuperscript{2}. Unfortunately, such an instrument does not exist\textsuperscript{3-5}.

The compliance measurement instrument that is closest to the requirements of a gold standard is electronic medication event monitoring. This method records time and date of opening and closing of the drug medication package through special microelectronic circuitry integrated in the cap of a pill-bottle (Aardex Ltd., Zug, Switzerland) and is known as the Medication Event Monitoring System (MEMS\textsuperscript{®})\textsuperscript{6,7}. With this method, a history of medication events, assumed to indicate dosing times, is created that can be compared to the prescribed dosing regimen. The method conforms to the definition of patient compliance: “the extent to which the actual dosing history conforms to the prescribed dosing regimen”\textsuperscript{8}. The advantages of electronic medication event monitoring are that it can provide accurate times of drug intake over a long period (up to 3 years), it is not invasive, and it does not require laboratory analyses. It is also not sensitive to “white-coat compliance,” the phenomenon wherein ordinarily poorly compliant patients dose correctly just before a clinical visit. The disadvantage of the instrument is of course that it is an indirect method, in that it does not prove drug intake, and it requires the assumption that every cycle of opening/closing of the pill-bottle signifies the prescribed dose was actually taken.

The assumption that each opening of the bottle truthfully indicates the taking of the pill has been discussed among authorities in the field of patient compliance research, with the conclusion that the assumption is likely to be accurate since it would require a very strong routine, combined with sustained malfeasance, for a patient to open the bottle at each scheduled dosing time for a long period of time without taking the tablet. At the same time all other methods to measure patient compliance are easily vulnerable to patient-initiated data-tailoring\textsuperscript{9,10,11}. Therefore we decided to validate the CQR against electronic medication event monitoring.

**MATERIALS AND METHODS**

The development of the CQR has been described in detail\textsuperscript{1}. It consists of 19 items, which were derived from a series of patient interviews and a focus group interview, and reflects statements that were made by individual patients regarding their drug-taking behavior (Appendix 1). Patients are asked to indicate how much they agree with each statement on a 4-point Likert scale, with anchors “don’t agree at all; 2. don’t agree; 3. agree; 4. agree very much.” *For gout patients, the word anti-rheumatic was changed to anti-gout.* **These items were recoded to compute a total score.**

**Instructions to the patient.**

On the next pages you will find a number of statements made by patients with a rheumatic disease. Please indicate for each statement how far you agree, by placing a circle around the number that reflects your opinion best.

1. If the rheumatologist tells me to take the medicines, I do so.
2. I take my anti-rheumatic* medicines because I then have fewer problems.
3. I definitely don’t dare to miss my anti-rheumatic medications.
4. If I can help myself with alternative therapies, I prefer that to what my rheumatologist prescribes**.
5. My medicines are always stored in the same place, and that’s why I don’t forget them.
6. I take my medicines because I have complete confidence in my rheumatologist.
7. The most important reason to take my anti-rheumatic medicines is that I can still do what I want to do.
8. I don’t like to take medicines. If I can do without them, I will**.
9. When I am on vacation, it sometimes happens that I don’t take my medicines**.
10. I take my anti-rheumatic drugs, for otherwise what’s the point of consulting a rheumatologist?
11. I don’t expect miracles from my anti-rheumatic medicines**.
12. If you can’t stand the medicines you might say: “throw it away, no matter what”**.
13. If I don’t take my anti-rheumatic medicines regularly, the inflammation returns.
14. If I don’t take my anti-rheumatic medicines, my body warns me.
15. My health goes above everything else and if I have to take medicines to keep well, I will.
16. I use a dose organizer for my medications.
17. What the doctor tells me, I hang on to.
18. If I don’t take my anti-rheumatic medicines, I have more complaints.
19. It happens every now and then, I go out for the weekend and then I don’t take my medicines**.

The answers are scored on a 4-point Likert scale with anchors: 1. don’t agree at all; 2. don’t agree; 3. agree; 4. agree very much. **For gout patients, the word anti-rheumatic was changed to anti-gout.** Therefore we decided to validate the CQR against electronic medication event monitoring.

For this validation study, permission was obtained from the Medical Ethical Committees of all 3 participating hospitals. We included all consenting consecutive outpatients at the outpatient rheumatology wards of the University Hospital Maastricht, Atrium Hospital Heerlen, and Maasland Hospital Sittard, respectively a primary-secondary and 2 primary referral centers for rheumatology.

Patients fulfilled the inclusion criterion of a diagnosis by a rheumatologist of RA, PMR, or gout. The following medications were included: For RA patients, sulfasalazine (prescribed twice daily after up-titration), methotrexate (prescribed once weekly), diclofenac (prescribed twice or thrice daily; combination with misoprostol was allowed), or naproxen (twice daily). For PMR patients, prednisone or prednisolone were included (in the analyses patients taking prednisone and prednisolone were combined). Gout patients were included if they started taking prophylactic daily colchicine, or allopurinol or benzbromaron (in the analyses patients taking allopurinol or benzbromaron were combined and categorized under “uric acid lowering agents”). For all groups prescriptions had to be first-prescriptions (note that this is not the same as new diagnoses) and had to be “taken as directed” (not “on demand”). In a case where 2 drugs were started at the same time (mostly for gout), the drug to monitor was chosen to be the drug group where the least number of patients were enrolled. Patients were to be responsible for taking their own medication and were therefore not included if a care-giver was involved in the patient’s taking of medication (e.g., in the case of a nursing home or hospitalized patients).
During the visit at the outpatient rheumatology ward, patients were informed by their rheumatologist about the purpose and requirements of the project and the characteristics of the MEMS system, so that patients were aware of the monitoring capability of the drug package, and signed the consent document. Each patient received a MEMS cap and pill-bottle, and his/her pharmacist was notified by fax that the patient was in a clinical study and was asked to transfer the prescribed medication to the pill-bottle. Patients also received the CQR, which they were asked to complete in the first week after starting medication. All patients received a followup telephone call by the investigator (EdK) about 3 days after the visit to the rheumatologist to answer further questions, and to ensure that the medication was indeed transferred to the MEMS bottle. No patient reported problems with transferring the medication to the MEMS bottle.

Six months (gout patients 12 months) after start of drug therapy, or sooner if withdrawal was deemed necessary because of lack of efficacy or side effects, patients were asked to complete the identical set of questionnaires again and to return the electronically monitored pill-bottle to the rheumatologist or investigator. In addition, patients were asked to request a medication history from their pharmacy. This is a computerized list noting all drugs and the date they were dispensed at the pharmacy. In The Netherlands the majority of patients are required by their health insurer to subscribe to one pharmacy, ensuring that virtually all dates of medication dispensing (and therefore extra openings to fill the bottles) were recorded.

The data of the MEMS were downloaded to a personal computer and processed by special software designed to analyze dosing histories (CSS v. 2.1; Aardex). If necessary, days of special openings of the pill-bottle (such as pharmacy visits or if the patient had recorded unnecessary openings) were marked as “non-monitored period.” These days were subsequently not used in the analyses. For example: a patient with 100 monitored days with 4 refill visits at the pharmacy would be analyzed with 96 monitored days.

Patient compliance was calculated as both taking compliance and correct dosing:

Taking compliance: the percentage of prescribed doses taken, calculated as: (total number of openings/total number of prescribed doses) × 100%. Example: a patient opened the MEMS cap 170 times while taking twice daily sulfasalazine for a monitored period of 100 days, so taking compliance = (170/200) × 100% = 85%.

Correct dosing: the percentage of days on which the correct number of doses was taken, calculated as: (total number of days with openings as prescribed/total number of monitored days) × 100%. Example: a patient opened the MEMS cap 170 times while taking twice daily sulfasalazine for a monitored period of 100 days, but only on 58 days were there 2 openings, during a monitored period of 100 days, so correct dosing = (58/100) × 100% = 58%.

Satisfactory compliance was arbitrarily defined as taking compliance or correct dosing > 80%. Unsatisfactory compliance was arbitrarily defined as taking compliance or correct dosing ≤ 80%.

Analyses consisted of descriptive statistics, Pearson correlation coefficients, multiple regression analyses, one-way analysis of variance (ANOVA), and (stepwise) discriminant analyses. Weights of the discriminant function were determined with prior probabilities computed from group sizes, and computed using the separate-group covariance matrix. The classification results of the discriminant analyses were computed into group sizes, and computed using the separate-group covariance matrix. The nant function were determined with prior probabilities computed from

RESULTS

In total 127 consenting consecutive patients of the outpatient wards were included. They consisted of 81 patients with RA who were monitored for nonsteroidal antiinflammatory drugs (13 diclofenac and 20 naproxen) or disease modifying antirheumatic drugs (DMARD; 25 sulfasalazine and 23 methotrexate), 17 patients with PMR who were monitored for prednisone or prednisolone, and 29 patients with gout who were monitored for colchicine (n = 12), allopurinol (10), or benzbromaron (7). Some basic descriptive demographic variables are shown in Table 1.

Twenty-three patients did not complete the CQR within 2 weeks after initiation of the new prescription. These patients were therefore excluded from the analysis. Of the remaining 104 patients, 85 completed all 19 questions, and 19 patients had a missing value for at least one of the 19 items. Questions 9 and 19 were missed most often. A comparison of compliance between the groups with 104 patients (all patients with an available CQR) and 85 patients (the group who completed the CQR with no missing values) showed no significant differences between taking compliance and correct dosing (Table 2). Since the development procedure of the CQR showed that there is no statistical justification to reduce the number of items below 19, and to ensure that the instrument was analyzed as designed, we used the dataset with all 85 patients who had a complete set of CQR data and MEMS data to analyze the validity of the CQR.

The mean CQR score was 76.6 (standard deviation 12.8). One-way ANOVA showed there were no statistical differences between the various treatment groups (F = 0.329, df = 6, df = 101, p = 0.92). Compliance as measured by the MEMS is summarized in Table 3. These data are reported in detail. However, multiple regression analyses with compli-
ance variables as independent variables and all 19 CQR items as dependent variables showed that the CQR items significantly and accurately predict taking compliance ($F = 2.91$, df = 19, df = 65, $p = 0.001$, $r^2 = 0.46$) and correct dosing ($F = 2.46$, df = 19, df = 65, $p = 0.004$, $r^2 = 0.42$). This indicates that the weighting scores assigned to the individual items in the multiple regression analyses are an important factor in the explanation of taking compliance and correct dosing.

A discriminant analysis was performed to test the predictive value of the CQR. The classification table of the calculated discriminant function (see Appendix 2 for the individual weights of the items, the critical cutting score, and an explanation) of the CQR versus MEMS data to detect taking compliance $\leq 80\%$ (Table 4) shows a sensitivity and specificity of $62\%$ ($95\%$ confidence interval $56.8, 67.3\%$) and $95\%$ ($95\%$ CI $92.2, 97.1\%$), respectively. The likelihood ratio for a positive test result (e.g., to detect taking compliance $\leq 80\%$) was 11.6 ($95\%$ CI $6.7, 20.1$).

Sensitivity and specificity to detect unsatisfactory correct dosing ($\leq 80\%$) was $89\%$ ($95\%$ CI $85.0, 91.9\%$) and $70\%$ ($95\%$ CI $64.7, 74.7\%$), respectively. The corresponding likelihood ratio to detect correct dosing $\leq 80\%$ is therefore 2.9 ($95\%$ CI $1.5, 5.9$).

The same analyses were performed to see how well the CQR was able to detect taking compliance and correct dosing $\leq 50\%$. The sensitivities were $63\%$ ($95\%$ CI $57.2, 67.8\%$) and $62\%$ ($95\%$ CI $56.6, 67.2\%$), the specificities were $97\%$ ($95\%$ CI $95.7, 99.1\%$) and $93.8\%$ ($95\%$ CI $91.1, 96.4\%$), respectively. The corresponding likelihood ratio to detect taking compliance $\leq 50\%$ was $24.1$ ($95\%$ CI $7.9, 73.1$), and to detect correct dosing $\leq 50\%$ was $9.9$ ($95\%$ CI $7.0, 14.0$).

The choices for compliance $\leq 80\%$ and $\leq 50\%$ are arbitrary and are based solely on our clinical judgment. We have summarized the performance for other detection levels of the CQR in terms of likelihood to detect low compliance in Figure 1. It is clear that the likelihood ratio rises with lower detection levels.

Four items were especially predictive for taking compliance, CQR questions 3 (I definitely don’t dare to miss my antirheumatic medications); 7 (The most important reason to take my antirheumatic medicines is that I can still do what I want to do); 5 (My medicines are always stored in the same place, and that’s why I don’t forget them); and 12 (If you can’t stand the medicines you might say: “throw it away, no matter what”) (combined $r^2 = 0.35$). This means that with these 4 items it is possible to explain 35% of the variance in taking compliance. The predictive values of these items are somewhat lower than predictive value of the full CQR-19: sensitivity $51.7\%$ ($95\%$ CI $46.3, 57.1\%$), specificity $87.5\%$ ($95\%$ CI $83.9, 91.1\%$), and the likelihood ratio for a positive test ratio was $4.1$ ($95\%$ CI $2.4, 7.0$).

**DISCUSSION**

The CQR is a patient oriented questionnaire that was designed to explore concepts related to patient compliance in antirheumatic drug regimens. It has several attractive properties: with 19 items it is a relatively short measure, and since it is heavily based on patients’ input during the development phase the items are easy to read, understand, and answer. Patients can complete the questionnaire in their own environment; a personal interviewer is not required. Mean time to complete was approximately 12 minutes. It has good psychometric properties, as reported.

In this validation study the performance of the CQR was compared against electronically measured taking compliance and correct dosing. The total CQR score did not correlate with either taking compliance or correct dosing. However, the discriminant analyses showed that it is possible to assign individual weights to each item, which allows the investigator to discriminate patients with relatively good “taking compliance” and “correct dosing” from those who do not comply very well.

To facilitate future use of the CQR in research, we have included 4 discriminant formulas, optimized to detect taking compliance $\leq 80\%$, $\leq 50\%$, and correct dosing $\leq 80\%$ and $\leq 50\%$ (Appendix 2). These discriminant formulas can be used in several ways: e.g., when screening for patients who are likely to comply suboptimally to antirheumatic drug therapy, perhaps as a prerandomization compliance screen in clinical trials. For drugs where compliance is especially important, such as new DMARD, it may be desirable to exclude these patients, or, in other instances, to prestratify them.

Interestingly, the stepwise discriminant analyses showed

### Table 3. Summary of compliance data determined by the Medication Event Monitoring System® (all percentages).

<table>
<thead>
<tr>
<th></th>
<th>Mean Taking Compliance, SD (95% CI)</th>
<th>Mean Correct Dosing, SD (95% CI)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen</td>
<td>82, 16 (75, 90)</td>
<td>68, 25 (57, 80)</td>
<td>20</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>77, 27 (61, 93)</td>
<td>67, 33 (47, 87)</td>
<td>13</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>72, 29 (60, 83)</td>
<td>55, 28 (44, 67)</td>
<td>25</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>107, 22 (98, 117)</td>
<td>81, 15 (75, 87)</td>
<td>23</td>
</tr>
<tr>
<td>Prednisone</td>
<td>96, 12 (89, 102)</td>
<td>88, 9 (83, 92)</td>
<td>17</td>
</tr>
<tr>
<td>Colchicine</td>
<td>65, 27 (48, 81)</td>
<td>44, 29 (26, 62)</td>
<td>12</td>
</tr>
<tr>
<td>Uric acid lowering drugs</td>
<td>84, 15 (76, 92)</td>
<td>74, 21 (63, 85)</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>85, 26 (80, 89)</td>
<td>69, 26 (64, 74)</td>
<td>127</td>
</tr>
</tbody>
</table>

### Table 4. 2 x 2 table with classification results of the discriminant analyses.

<table>
<thead>
<tr>
<th>CQR Prediction Function</th>
<th>Taking Compliance (MEMS)</th>
<th>Good</th>
<th>Sum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsatisfactory</td>
<td>18</td>
<td>3</td>
<td>21</td>
</tr>
<tr>
<td>Good</td>
<td>11</td>
<td>53</td>
<td>64</td>
</tr>
<tr>
<td>Sum</td>
<td>29</td>
<td>56</td>
<td>85</td>
</tr>
</tbody>
</table>

MEMS: the Medication Event Monitoring System®.
Appendix 2. Clarification of discriminant function

The CQR consists of 19 individual items. The variable to test against is taking compliance, defined in a binary form as taking compliance ≤ 80% (indicating insufficient compliance) and taking compliance > 80% (good taking compliance), where xx can be any value between 0 and 100.

The discriminant analysis involves deriving an equation of the following form:

\[ Z_k = a + W_1X_{1k} + W_2X_{2k} + \ldots + W_{19}X_{19k} \]

where \( Z_k \) = discriminant Z score for patient k; \( a \) = intercept; \( W_i \) = discriminant weight; \( X_{ik} \) = CQR score for item 1 and patient k.

The discriminant function for the CQR against taking compliance ≤ 80% and taking compliance > 80% was determined to be: \( Z_k = -3.478 - (0.445*item01) - (0.952*item02) + (1.676*item03) - (0.210*item04) + (0.024*item05) - (0.535*item06) + (0.003*item07) + (0.014*item08) - (0.011*item09) - (0.255*item10) + (0.102*item11) + (0.115*item12) + (0.025*item13) + (0.109*item14) + (0.447*item15) + (0.228*item16) + (0.535*item17) - (0.419*item18) + (0.683*item19). \)

Thus, if for an individual patient the values of \( X_1, X_2, X_3, \ldots \), etc., were replaced by his/her CQR scores, a score \( Z_k \) is obtained. If \( Z_k \) is below the \( Z_{CUT} \) of –0.5849, the patient is predicted to be in the group of taking compliance ≤ 80%; if \( Z_k \) is greater than \( Z_{CUT} \), the patient is predicted to be in the group of taking compliance > 80%.

Using the discriminant function, a 2 x 2 table can be computed (Table 4, main text).

Since the CQR is designed to detect low compliance, the desired test result is to detect taking compliance ≤ 80%. Sensitivity to detect taking compliance ≤ 80% is: 18/(18 + 11) x 100% = 62.1%. Specificty to detect taking compliance ≤ 80% is: 53/(53 + 3) x 100% = 94.6%.

The predictive value to detect low taking compliance ≤ 80% is: 18/18(18 + 3) x 100% = 85.7%. Similarly, predictive value to detect good taking compliance > 80% is: 53/(53 + 3) x 100% = 82.8%. The likelihood ratio to detect low taking compliance is represented by (sensitivity)/(100 – specificity) = 62.1/5.4 = 11.4.

To help the reader to use the classification results of the CQR in a variety of situations, the discriminant weights for the individual CQR items to detect taking compliance ≤ 80%, correct dosing ≤ 80%, taking compliance ≤ 50%, and correct dosing ≤ 50%, as well as the critical cutting scores are given (Table, next column).

Table. Discriminant weights for 4 CQR prediction functions.

<table>
<thead>
<tr>
<th>CQR Item</th>
<th>Taking Compliance ≤ 80%</th>
<th>Taking Compliance ≤ 50%</th>
<th>Correct Dosing ≤ 80%</th>
<th>Correct Dosing ≤ 50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Constant)</td>
<td>-3.4777</td>
<td>-0.0294</td>
<td>-5.3088</td>
<td>-2.6171</td>
</tr>
<tr>
<td>1</td>
<td>-0.4448</td>
<td>-0.1530</td>
<td>-1.2897</td>
<td>-0.4475</td>
</tr>
<tr>
<td>2</td>
<td>-0.9517</td>
<td>-1.1213</td>
<td>-0.1453</td>
<td>-0.3557</td>
</tr>
<tr>
<td>3</td>
<td>1.6758</td>
<td>1.1975</td>
<td>1.2362</td>
<td>1.8116</td>
</tr>
<tr>
<td>4</td>
<td>-0.2101</td>
<td>-0.4300</td>
<td>0.3197</td>
<td>-0.0317</td>
</tr>
<tr>
<td>5</td>
<td>0.0244</td>
<td>-0.1251</td>
<td>0.7938</td>
<td>0.1827</td>
</tr>
<tr>
<td>6</td>
<td>-0.5353</td>
<td>-1.0975</td>
<td>-0.0142</td>
<td>-0.9797</td>
</tr>
<tr>
<td>7</td>
<td>0.0030</td>
<td>0.5287</td>
<td>0.1136</td>
<td>-0.2690</td>
</tr>
<tr>
<td>8</td>
<td>0.0135</td>
<td>0.0389</td>
<td>0.1321</td>
<td>-0.2455</td>
</tr>
<tr>
<td>9</td>
<td>-0.0106</td>
<td>-0.0301</td>
<td>-0.0999</td>
<td>0.0399</td>
</tr>
<tr>
<td>10</td>
<td>-0.2546</td>
<td>-0.0048</td>
<td>-0.0640</td>
<td>-0.1436</td>
</tr>
<tr>
<td>11</td>
<td>0.1023</td>
<td>0.0344</td>
<td>0.2135</td>
<td>0.1329</td>
</tr>
<tr>
<td>12</td>
<td>0.1155</td>
<td>0.1613</td>
<td>0.1795</td>
<td>0.0738</td>
</tr>
<tr>
<td>13</td>
<td>0.0248</td>
<td>-0.0413</td>
<td>0.1246</td>
<td>-0.3445</td>
</tr>
<tr>
<td>14</td>
<td>0.1091</td>
<td>-0.1884</td>
<td>0.2075</td>
<td>0.1946</td>
</tr>
<tr>
<td>15</td>
<td>0.4475</td>
<td>0.0900</td>
<td>-0.1535</td>
<td>0.2179</td>
</tr>
<tr>
<td>16</td>
<td>0.2284</td>
<td>0.1318</td>
<td>-0.0269</td>
<td>0.1442</td>
</tr>
<tr>
<td>17</td>
<td>0.5350</td>
<td>0.4040</td>
<td>0.3362</td>
<td>0.3698</td>
</tr>
<tr>
<td>18</td>
<td>-0.4191</td>
<td>0.0529</td>
<td>-0.6158</td>
<td>-0.4663</td>
</tr>
<tr>
<td>19</td>
<td>0.6829</td>
<td>0.6527</td>
<td>0.4234</td>
<td>0.9168</td>
</tr>
</tbody>
</table>

Critical cutting score = -0.5849

In addition, we have created a Microsoft Excel spreadsheet that is designed to help the user calculate the discriminant function from the raw CQR scores for taking compliance and correct dosing cutoff values between 95% and 50%. It is freely available via the first author (erik@project.demon.nl) and can also be downloaded from the World Wide Web (www.project.demon.nl/CQR) [cited June 11, 2003].

be used as a quick checklist in the mind of the physician who is trying to assess the risk of unsatisfactory compliance. Perhaps further research can also validate the use of such a short checklist in the clinical assessment for a compliance support program.

If more precision is required, one could use the CQR as a formal diagnostic instrument in everyday clinical care in patients with a lack of clinical response to antirheumatic therapy, to distinguish between inadequate compliance and pharmacologic nonresponse. Doing so may prevent needless escalation of the dose or change of drug. The specific answers to the questions may provide clues to overcome the compliance problem.

Furthermore, the CQR could have a place in compliance-intervention strategies such as measurement-guided intervention15-17, where it can provide useful insight into the reasons and factors underlying patient compliance/noncompliance (which the electronic monitors cannot). This approach, when carefully applied to patients who have a problem in complying satisfactorily with prescribed drug regimens, has shown promising results in other fields15-17, but to our knowledge has not been tested yet in rheuma-
ology. We are investigating this application of the CQR in a project evaluating a compliance enhancing intervention in patients with RA.

A final use of the CQR could be to employ electronic medication event monitoring more cost effectively in routine clinical practice. The monitors have so far mostly been used in clinical trials, but could be valuable in routine daily practice as a diagnostic instrument to detect whether nonresponse is due to noncompliance or pharmacologic nonresponse, and as a tool to improve compliance by giving patient and healthcare provider insight into the dosing history. It seems logical (but is so far not proven) that a compliance intervention is most useful in patients who have low compliance to start with. The CQR could be used to prescreen these patients, minimizing the use of monitors in patients who are good compliers from the outset of their treatment.

Some may find it cumbersome to use a discriminant function, which requires incorporating the weights for the 19 items and a critical cutting score. We have therefore created a Microsoft Excel spreadsheet in which all weights and critical cutting scores for a variety of scenarios are precalculated. The spreadsheet is easy to use, and is freely available from the first author or from the World Wide Web (Appendix 2).

A special concern in the use of the CQR is missing values. In our sample, there were 19 patients out of 104 with at least one missing value for one of the 19 CQR questions (18%). One possible explanation is that the CQR items that were missed most often, questions 9 and 19 (Appendix 1), which ask about holidays and special weekends, are not applicable to some patients and therefore they leave the answer box open. One could hypothesize that these patients differ in compliance from those who do complete the questionnaire. This was not confirmed by analysis, however (Table 2). It is clear that when applying the CQR, the importance of completing all 19 items must be stressed.

These results support the validity of the CQR. The high predictive values of the CQR suggest that it might be useful as a screening instrument.

ACKNOWLEDGMENT
We thank the participating rheumatologists for kindly including patients in the study: Maarten Boers, Marijke van Santen, Henk Goei-The, Harry Houben, Robert Landewé, Anneke Spoorenberg, Liesbeth Heuff-Doorenbosch, Peter Dubbeld, Mike de Jager, Wilfried van der Weele, Hans Groenendael, and Christine Langenaken. Also, we thank John Urquhart for his contributions and support to this study, as well as for reviewing this manuscript.

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