Evaluation of clinically relevant changes in patient-reported outcomes in knee and hip osteoarthritis: the Minimal Clinically Important Improvement

Florence Tubach, Philippe Ravaud, Gabriel Baron, Bruno Falissard, Isabelle Logeart, Nicholas Bellamy, Claire Bombardier, David T Felson, Marc C Hochberg, Désirée van der Heijde, and Maxime Dougados

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Title: Evaluation of clinically relevant changes in patient-reported outcomes in knee and hip osteoarthritis: the Minimal Clinically Important Improvement

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ABSTRACT

In clinical trials, at the group level, results are usually reported as mean and standard deviation of the change in score, which is not meaningful for most readers.

Objective: To determine the Minimal Clinically Important Improvement (MCII) of pain, patient’s global assessment of disease activity and functional impairment in patients with knee and hip osteoarthritis.

Methods: We conducted a prospective multicenter cohort study of 4–weeks’ duration involving 1,362 outpatients with knee or hip osteoarthritis. Data on assessment of pain and patient’s global assessment, measured on visual analog scales (VAS), and functional impairment, measured on the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) function subscale, were collected at baseline and final visits. Patients assessed their response to therapy on a 5-point Likert scale at the final visit. An anchoring method based on the patient’s opinion was used. The MCII was estimated in a subgroup of 814 patients (603 with knee osteoarthritis and 211 with hip osteoarthritis).

Results: For knee and hip osteoarthritis, MCII for absolute (and relative) changes are, respectively: 1) -19.9 mm (-40.8%) and -15.3 mm (-32.0%) for pain, 2) -18.3 mm (-39.0%) and -15.2 mm (-32.6%) for patient’s global assessment 3) -9.1 (-26.0%) and -7.9 (-21.1%) for WOMAC function subscale score. The MCII is affected by the initial degree of symptoms but not by age, disease duration or gender.

Conclusion: Using such criteria as MCII in clinical trials would provide meaningful information to interpret the results by expressing them as a proportion of improved patients.

Word count: 248

Key words: functional impairment; hip osteoarthritis; knee osteoarthritis; outcome criteria; response to therapy
The choice of an outcome measure is a major step in the design of clinical trials. In evaluating the symptomatic severity of osteoarthritis of the lower limbs, scientific groups such as the OMERACT (Outcome Measures in Rheumatology group), GREES (Group for the Respect of Ethics and Excellence in Science), and OARSI (OsteoArthritis Research Society International) have raised the importance of evaluating at least three dimensions: pain, patient’s global assessment of disease status, and functional impairment. At the individual level, determining the minimal meaningful change in a score with use of a structured instrument is a challenge. Are changes in self-reported levels of pain of 10 mm on a 0-100 mm visual analogue scale (VAS) clinically important? Does the change reflect meaningful improvement for the patient? The concept of the Minimal Clinically Important Difference (MCID) could help in interpreting changes in scores at the individual level. However, the MCID, which could reflect either an improvement or a worsening, has not been used here, since in clinical trials we are always interested in improvement and not worsening. Furthermore, it has been shown that the MCID could be different for improvement and worsening. The Minimal Clinically Important Improvement (MCII), defined as the smallest change in measurement that signifies an important improvement in a patient’s symptom, seems more appropriate and, in clinical trials, provides readers with additional information on the effect size by expressing the results more meaningfully (i.e., percentage of improved patients).

The aim of this prospective cohort study was to estimate the MCII from the patient’s perspective for three main patient-reported outcomes used in osteoarthritis trials: pain, patient’s global assessment of disease activity, and functional impairment.

MATERIALS AND METHODS

STUDY DESIGN
We conducted a prospective cohort study of 4 weeks’ duration.

STUDY POPULATION
This study involved 1,362 outpatients with knee or hip osteoarthritis, as defined by the American College of Rheumatology, included by 399 rheumatologists. Each rheumatologist had to include four patients, three with knee osteoarthritis and one with hip osteoarthritis. To be included in the study, patients had to experience pain from osteoarthritis (≥ 30 mm on a VAS varying from 0 to 100 [0-100 mm VAS]), require treatment with a nonsteroid anti-inflammatory drug (NSAID), and be able to complete questionnaires in French. Inclusion could begin with the onset of treatment or a switch from one NSAID to another. Patients were excluded if they had a prosthesis on the assessed joint or if they had been treated by intra-articular injection in the 4 weeks before the study began. All patients initially visited the rheumatologist in charge of the patient, and an NSAID was prescribed (the drug and its dosage was chosen by the physician). A final visit to the same rheumatologist was scheduled 4 weeks later.

MEASUREMENTS
At the baseline visit, demographic and disease data were collected. Patients assessed their status regarding osteoarthritis at the baseline and final visits. They assessed the following patient-reported outcomes: 1) Pain on movement during the 48 hours before the visit, measured on a 0–100-mm VAS; 2) global assessment of disease activity measured on a 0–100-mm VAS; and 3) physical function, measured on the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) function subscale (17 items, 5-point Likert
scale for each item; high scores indicate high degree of functional impairment; total score normalized to a 0–100 score).

At the final visit, a random sample of two-thirds of the patients (n=923) assessed their response to NSAID therapy on a 5-point Likert scale (none = no good at all, ineffective drug; poor = some effect but unsatisfactory; fair = reasonable effect but could be better; good = satisfactory effect with occasional episodes of pain or stiffness; excellent = ideal response, virtually pain free). The other third of the patients assessed their response to therapy on a 15-point Likert scale (from -7, a very great deal worse, to +7, a very great deal better, with 0, no change).

STATISTICAL ANALYSIS

All the analyses considered patients with knee and hip osteoarthritis separately. The MCII was determined in the subgroup of 814 patients (603 with knee and 211 with hip osteoarthritis) whose assessment of response to therapy was measured on a 5-point Likert scale and who had completed the final visit.

An anchoring method based on the patient’s assessment of response to therapy was used. The MCII was estimated for both the absolute (final value – baseline value) and the relative (valuebaselinevalue final − baseline value ) changes in each patient-reported outcome. It was estimated by constructing a curve of cumulative percentages of patients as a function of the change in score (e.g., difference in pain score) among patients whose final evaluation of response to therapy was “good, satisfactory effect with occasional episodes of pain or stiffness”, because we wanted to focus on the improvement that was clinically important. Logistic regression was used to model the observations (Fig. 1). We targeted the point at the flattening of the curve at which most subjects stated they had improved. To determine the change in score corresponding to this point, we first looked at the 2-parameter logistic model that best fit the data. Then we determined the square root of the third derivative of this logistic function that corresponded to the MCII. One can demonstrate that this point corresponds by construction to the 78.9th percentile of the change in score, and thus we propose to define the MCII as the 75th percentile of the change in score, because it is very close to the point defined above and easier to derive. The model permitted us first to determine that the target point was correctly approached by the 75th percentile and second to estimate the 95% confidence intervals.

In a second step, we stratified the analysis on the baseline score of interest (divided into tertiles) to assess whether the level of pain, the patient’s assessment of disease activity and functional impairment had a modifying effect on the MCII. That is we stratified 1) on the baseline pain score to estimate the MCII for pain; 2) on the baseline assessment of disease activity to estimate the MCII for patient’s assessment of disease activity; 3) on the baseline WOMAC function score to estimate the MCII for functional impairment.

In a third step, to investigate the effect of covariates (other than location of osteoarthritis) on the MCII, we stratified the analysis successively by age, disease duration (both divided into tertiles) and gender.

Statistical analyses was performed with use of the SAS Release 8.2 statistical software package and the Splus 4.5 statistical software package.

COMPLIANCE WITH RESEARCH ETHICS STANDARDS

This study has been conducted in compliance with the protocol, the Good Clinical Practices and the Declaration of Helsinki principles.
RESULTS
A total of 1,362 patients were enrolled in the study: 1,019 (75%) had knee and 343 (25%) hip osteoarthritis; 913 were females (67%); and the mean age was 67.2 years (S.D. 10.5). A total of 914 (90%) patients with knee and 310 (90%) with hip osteoarthritis completed the final visit. Patients lost to follow up were excluded from the analysis. Patients lost to follow up did not differ from completers in terms of baseline characteristics. Among the completers, 603 patients with knee and 211 with hip osteoarthritis assessed their response to therapy on a 5 point-Likert scale.

The descriptive statistics on clinical and demographics variables are shown in Table 1.

Table 1. Baseline characteristics of patients.

<table>
<thead>
<tr>
<th></th>
<th>Knee osteoarthritis (n=603)</th>
<th>Hip osteoarthritis (n=211)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67.9</td>
<td>10.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.5</td>
<td>13.8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163.8</td>
<td>8.5</td>
</tr>
<tr>
<td>Body Mass Index (kg.m²)</td>
<td>28.1</td>
<td>4.8</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>4.7</td>
<td>5.8</td>
</tr>
<tr>
<td>Pain score (0–100-mm VAS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>59.3</td>
<td>16.2</td>
</tr>
<tr>
<td>Change (Week 0 – Week 4)</td>
<td>-24.9</td>
<td>21.5</td>
</tr>
<tr>
<td>Patient global assessment (0–100-mm VAS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>59.6</td>
<td>18.3</td>
</tr>
<tr>
<td>Change (Week 0 – Week 4)</td>
<td>-24.7</td>
<td>24.0</td>
</tr>
<tr>
<td>WOMAC function score (0-100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>42.8</td>
<td>16.1</td>
</tr>
<tr>
<td>Change (Week 0 – Week 4)</td>
<td>-11.6</td>
<td>13.9</td>
</tr>
</tbody>
</table>
Knee osteoarthritis (n=603)  

<table>
<thead>
<tr>
<th>Gender</th>
<th>n</th>
<th>%</th>
<th>Hip osteoarthritis (n=211)</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>421</td>
<td>69.8</td>
<td></td>
<td>133</td>
<td>63.0</td>
</tr>
<tr>
<td>Kellgren &amp; Lawrence grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>108</td>
<td>17.9</td>
<td></td>
<td>33</td>
<td>15.7</td>
</tr>
<tr>
<td>III</td>
<td>268</td>
<td>44.4</td>
<td></td>
<td>111</td>
<td>52.9</td>
</tr>
<tr>
<td>IV</td>
<td>227</td>
<td>37.7</td>
<td></td>
<td>66</td>
<td>31.4</td>
</tr>
<tr>
<td>NSAID* intake during past 4 weeks</td>
<td>178</td>
<td>29.7</td>
<td></td>
<td>69</td>
<td>32.7</td>
</tr>
<tr>
<td>Analgesic treatment**</td>
<td>344</td>
<td>57.2</td>
<td></td>
<td>141</td>
<td>67.1</td>
</tr>
<tr>
<td>Symptomatic slow-acting drug intake***</td>
<td>209</td>
<td>34.8</td>
<td></td>
<td>90</td>
<td>42.9</td>
</tr>
</tbody>
</table>

* nonsteroid anti-inflammatory drugs (before the start of the study)
** other than NSAIDs (before the start of the study)
*** chondroitine sulfate, diacerheine, or avocado/soybean unsaponifiables

VAS: visual analog scale

Patients’ rating of response to therapy is shown in Figure 2.

The MCII values for the three patient-reported outcomes, according to location of osteoarthritis, are listed in Table 2. These values were estimated in the 265 patients with knee and the 87 patients with hip osteoarthritis who completed the final visit and assessed their response to therapy as “good”. For instance, patients with knee osteoarthritis considered themselves clinically improved if the decrease in pain exceeded 19.9 mm on the 0–100-mm VAS. We used the data from the 5-point not the 15-point Likert scale mentioned in the Methods section.

Table 3 shows the estimates of the MCII (for absolute change) stratified on the baseline score in patients with knee or hip osteoarthritis. The higher the baseline score, the larger the MCII. Patients dealing with a severe symptom need a higher level of change to consider themselves clinically improved than those with lighter symptoms. For instance, patients with severe pain (a high tertile of baseline pain score) considered themselves clinically improved if the decrease in pain exceeded 36.6 mm on the 0–100-mm VAS. Patients with lighter pain (low tertile of baseline pain score) needed a lower level of change (-10.8 mm on the VAS) to consider themselves clinically improved. The estimates of the MCII for relative change also varied across tertiles of the baseline score (data not shown). The estimates of the MCII do not vary across age, disease duration tertiles or gender (data not shown).
Table 2: Minimal Clinically Important Improvement (MCII) scores according to patients' location of osteoarthritis. The MCII was defined as the 75th percentile of the change in score among patients whose evaluation of response to therapy was “good”, in terms of three patient-reported outcomes: pain, as assessed on a visual analogue scale (VAS); global assessment of disease status, on a VAS; or the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) function subscale score.

<table>
<thead>
<tr>
<th>Patient-reported outcomes</th>
<th>Knee osteoarthritis</th>
<th>Hip osteoarthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absolute change</td>
<td>Relative change</td>
</tr>
<tr>
<td></td>
<td>MCII [95% CI]</td>
<td>MCII [95% CI]</td>
</tr>
<tr>
<td>Pain (0–100-mm VAS)</td>
<td>-19.9 mm [-21.6 ; -17.9]</td>
<td>-40.8% [-44.8 ; -36.1]</td>
</tr>
<tr>
<td>Patient global assessment (0–100-mm VAS)</td>
<td>-18.3 mm [-19.8 ; -16.7]</td>
<td>-39.0% [-45.8 ; -30.6]</td>
</tr>
<tr>
<td>WOMAC function score (0-100)</td>
<td>-9.1 [-10.5 ; -7.5]</td>
<td>-26.0% [-28.6 ; -23.3]</td>
</tr>
</tbody>
</table>
Table 3. Minimal Clinically Important Improvement (MCII) score of absolute change in patients with knee or hip osteoarthritis, by low, intermediate and high baseline score tertiles. The MCII was defined as the 75th percentile of the change in score among patients whose evaluation of response to therapy was “good”, in terms of three patient-reported outcomes: pain, as assessed on a visual analogue scale (VAS); global assessment of disease status on a VAS; or the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) function subscale score.

<table>
<thead>
<tr>
<th></th>
<th>Knee osteoarthritis</th>
<th>Hip osteoarthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline score tertile</td>
<td>Baseline score tertile</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>Intermediate</td>
</tr>
<tr>
<td><strong>MCII score (95% CI, tertile range)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pain (0–100-mm VAS)</strong></td>
<td>-10.8 mm [-12.7 ; -8.7]</td>
<td>-27.4 mm [-29.7 ; -24.6]</td>
</tr>
<tr>
<td></td>
<td>30 to 51.0</td>
<td>51.1 to 66.2</td>
</tr>
<tr>
<td><strong>Patient's global assessment of disease (0–100-mm VAS)</strong></td>
<td>-6.4 mm [-8.6 ; -3.8]</td>
<td>-24.6 mm [-26.8 ; -22.1]</td>
</tr>
<tr>
<td></td>
<td>≤ 50.4</td>
<td>50.5 to 68.7</td>
</tr>
<tr>
<td><strong>WOMAC function score (0-100)</strong></td>
<td>-5.3 [-6.5 ; -3.8]</td>
<td>-11.8 [-13.0 ; -10.4]</td>
</tr>
<tr>
<td></td>
<td>≤ 35.3</td>
<td>35.4 to 51.5</td>
</tr>
</tbody>
</table>
DISCUSSION

This study dealt with the clinical meaningfulness of changes observed for patient-reported outcome measures. Because a statistically significant difference is mostly a matter of sample size, the most difficult issue is whether an observed or estimated difference is clinically important. In other words, statistical significance is not equivalent to clinical significance. Reporting results of a trial with use of MCII (i.e., as a percentage of improved patients) provides readers with more easily understood values and additional information to help them decide whether a treatment should be used. This threshold also allows for monitoring individual response to therapy over time and adapting treatment at the individual level (e.g., determining whether to initiate or interrupt a treatment). Furthermore, the designation and use of MCII in clinical trials is critical for meaningful systematic reviews and combining results from different studies in meta-analyses. This concept aims to complement, not replace, information on the effect size, since the effect size remains a more powerful approach.

The MCII is the smallest change in measures that signify an important improvement in a patient’s symptom. Thus, the MCII can undoubtedly be considered as a treatment target in the patient’s perspective. It is based on the patient’s opinion as an external anchor and contrasts changes within patients at the individual level (proportion of improved patients) instead of at the group level (mean change in a variable).

Approaches such as investigator-defined (expert consensus) or statistically defined methods have been used to determine this threshold. Despite the absence of a criterion measure, establishing the meaning of changes in a measure requires an independent standard. Patient global ratings are recommended as an external anchor for evaluating the clinical significance of individual change. The large sample of patients as experts in determining improvement is a good indicator of representativeness.

To determine the MCII, the external criterion was the patient’s assessment of response to therapy as assessed on a 5-point Likert scale. We defined MCII in the group of patients whose evaluation of response to therapy was “good”, because one is always looking for clinically important differences. We did not include patients whose evaluation of response to therapy was “excellent,” since our target was the minimal change important in the patient’s perspective. But obviously, this choice was arbitrary and affects the results (data not shown). The group of patients in whom MCII is determined and the wording of the items in the questionnaire to assess response to therapy should be chosen with the help of experts; in our study, the group of patients were chosen by the experts NB, CB, DF, MH, DvdH, and MD.

In a previous study, a 3 round Delphi method involving 6 academic rheumatologists experienced in osteoarthritis trials was used to define minimum clinically important differences (MCID) for some outcome measures used in osteoarthritis trials (not specifically focusing on hip or knee osteoarthritis). The MCID for patient pain on movement (measured on a 0-100 VAS) was 17.5 and that for patient global assessment of disease activity (measured on a 0-100 VAS) was 15. Although this method differs from that used in our study, the values are very close to our estimates of MCII for these patient-reported outcomes. The only study addressing meaningful change for the WOMAC Index dealt with the Minimal Clinically Perceptible Difference (MCPD), not the MCID.

Our study has demonstrated that the MCII varies depending on the baseline state. Patients dealing with most severe symptoms have to experience a greater change to consider themselves improved. Riddle and colleagues also found this effect in their investigation of
low back pain, where the MCID varied between 3 and 13 depending on the baseline range of scores (on the Roland Morris Back Pain Questionnaire, total score varying from 0 to 24 points, with baseline scores divided in 5 approximately equal-sized intervals). However, the precision of their estimates may have been compromised by the small sample size, especially for patients with high levels of disability. The variation of MCII across tertiles of baseline scores in our study cannot been imputed to the size of the sample, as confirmed by the narrowness of the 95% confidence intervals. We believe that this variation depending on the baseline score may preclude the use of the crude MCII. The patient’s initial or previous score should be taken into account when making decisions about important change. We propose to use three estimates of MCII corresponding to the tertiles of each baseline score to express the changes in terms of important improvement. This meets the recommendation of Crosby and associates for estimating MCID in health-related quality of life (HRQOL) criteria: to anchor baseline severity of individual patients.

We believe this is the first study to investigate the effect of several covariates such as age, gender, osteoarthritis location and disease duration on patient responses. It is interesting to observe that these factors do not consistently modify the estimates of MCII.

In conclusion, use of the concept MCII facilitates the presentation and interpretation of results obtained in clinical trials and the transposition of trial results into practice. However, it should take into account the baseline score. Further studies involving different data sets, clinical environments, languages, and countries, are necessary to validate these observations prospectively.

ACKNOWLEDGMENTS

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REFERENCES

Among patients considering their response to therapy as good on a 5-point Likert scale, 75% experienced a decrease in pain score between baseline and final visit upper than 19.9 mm on a 0-100 mm VAS (a change between −100mm and −19.9mm).
Figure 2: Distribution of patients’ assessment of their response to therapy

<table>
<thead>
<tr>
<th>Response to therapy</th>
<th>Knee osteoarthritis</th>
<th>Hip osteoarthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>5.6</td>
<td>6.2</td>
</tr>
<tr>
<td>Poor</td>
<td>11.9</td>
<td>15.2</td>
</tr>
<tr>
<td>Fair</td>
<td>32.7</td>
<td>30.8</td>
</tr>
<tr>
<td>Good</td>
<td>44.1</td>
<td>42.2</td>
</tr>
<tr>
<td>Excellent</td>
<td>5.7</td>
<td>5.6</td>
</tr>
</tbody>
</table>

Percentage of patients
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