

# Minimal clinically important improvement/difference (MCII/MCID) and patient acceptable symptom state (PASS): what do these concepts mean?

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An increasing focus has over recent years been directed to the use of categorical endpoints to define response, i.e. to define cut-points for important improvement and/or acceptable clinical state. The levels of Minimal Clinically Important Improvement (MCII) are typically defined according to the patients perception of what is an important improvement. It can be defined as the smallest change in measurement that signifies an important improvement. MCII signifies an improvement of relevance in a clinical trial, or the minimal meaningful change at an individual level. The Minimal Clinically Important Difference (MCID) may reflect either an improvement or a worsening. Patient Acceptable Symptom State (PASS) has been defined as the highest level of symptom beyond which patients consider themselves well. Cut-points for MCII and PASS are usually identified through two different statistical approaches. The 75th percentage approach identifies the cut-point corresponding to the 75 percentile of the scores for improvement in patients who report an important improvement by the anchoring question. Applying receiver operating characteristic (ROC) curves allows for choosing the threshold that is the best compromise between sensitivity and specificity for each outcome criterion.

The identified cut-points for MCII and PASS may easily be incorporated as endpoints in clinical trials, and will provide information about the proportion of patients that achieve an improvement exceeding the level accepted as MCII and achieve a state accepted as PASS.

Outcome measures used in rheumatoid arthritis (RA) and related diseases are usually classified into three main categories: measures that primarily capture information about the inflammatory activity, measures of structural damage and measures of health-related quality of life (HRQoL). Patient reported outcome measures are used to report HRQoL. Researchers and clinicians are usually focused on changes that occur during an intervention. Continuous measures are statistically more powerful than dichotomised outcomes when the objective is to discriminate between two interventions, such as active treatment versus placebo. However, clinicians may have problems communicating the result in an understandable way to the patient, for example, "based on results from clinical studies, with treatment A you will on average expect to have 10 mm more improvement in your pain as reported on a visual analogue scale compared to treatment B".

Over the last few years an increasing focus has been directed to the use of categorical end points to define response, that is, to define cut-off points for important improvement. For the patient (and the clinician) it is more clinically relevant and understandable to express the results in percentages, for example, "with treatment A you have a 40% probability of achieving an important treatment response compared to 20% with treatment B".

The question is then, what is an important response and who is going to define it? Second, for the patient, it is important to be better, but it is even more important to assess the chance of being good or to achieve an acceptable symptom state.<sup>1</sup> These concepts of change and state are important since they enable us to present results from therapeutic trials at an individual level.

## THE CONCEPTS OF MCII AND MCID

The American College of Rheumatology (ACR) response rate is the mostly widely used categorical response variable that

provides information about the proportion of patients with RA who develop important improvement. ACR20 indicates a 20% improvement in joint counts and three out of five other measures within the ACR core set of disease activity measures. ACR50 and ACR70 correspond to 50% and 70% improvement, respectively. Similar constructs of important improvement have also been developed for ankylosing spondylitis (AS) and osteoarthritis (OA).

The EULAR response criteria also report the proportion of patients with an improvement exceeding a value of change in DAS28, but achievement of a certain level of health state is also required. Thus, the EULAR response criteria capture aspects of both important improvement and achievement of a low inflammatory state.

The levels of Minimal Clinically Important Improvement (MCII) are typically defined according to the patient's perception of what is an important improvement. It can be defined as the smallest change in measurement that signifies an important improvement.<sup>2</sup> Different methods exist for identification of levels that reflect MCII<sup>3,4</sup> and the OMERACT initiative has also had a strong focus on the concept and the methodology.<sup>5</sup> The most widely used methodology in rheumatology has been to use an external anchoring question for identification of cut-off points for MCII, in other words, a question that asks the patient about perceived improvement.<sup>2,4,6</sup> Thus, MCII signifies an improvement of relevance in a clinical trial, or the minimal meaningful change at an individual level. The Minimal Clinically Important Difference (MCID) may reflect either an

**Abbreviations:** AS, ankylosing spondylitis; HRQoL, health-related quality of life; MCID, Minimal Clinically Important Difference; MCII, Minimal Clinically Important Improvement; OA, osteoarthritis; PASS, Patient Acceptable Symptom State; RA, rheumatoid arthritis; ROC, receiver operating characteristic; VAS, visual analogue scales

**Table 1** Identified PASS cut-off points for pain visual analogue scales (mm) in different chronic rheumatic diseases

	75th percentile approach	ROC approach
RA <sup>8</sup>	36	35
Knee OA <sup>10</sup>	32	
Hip OA <sup>10</sup>	35	
AS <sup>7</sup>	50	35
AS <sup>11</sup>	33	

AS, ankylosing spondylitis; OA, osteoarthritis; RA, rheumatoid arthritis; ROC, receiver operating characteristic

improvement or a worsening, and is thus less useful in settings where we are looking for improvement.

Two different statistical approaches are used to identify cut-off points for MCII when an external anchoring question is being used. The 75th percentage approach has been most extensively validated and widely used in rheumatology settings.<sup>2</sup> This approach identifies the cut-off point corresponding to the 75th percentile of the scores for improvement in patients who report an important improvement by the anchoring question. Applying receiver operating characteristic (ROC) curves allows for choosing the threshold that is the best compromise between sensitivity and specificity for each outcome criterion.<sup>7, 8</sup>

## THE PASS CONCEPT

Patient Acceptable Symptom State (PASS) has been defined as the highest level of symptom beyond which patients consider themselves well. The most widely used anchoring question to identify PASS cut-off points is, "Taking into account all the activities you have during your daily life, your level of pain, and also your functional impairment, do you consider that your current state is satisfactory?". The response options are "yes" or "no". An alternative wording is, "Taking into account your level of pain and also your functional impairment, if you were to remain for the next few months as you are today, would you consider that your current state is satisfactory?".<sup>9</sup> However, the wording is still being explored at the OMERACT meetings.<sup>4, 6</sup>

Recent studies have shown that the level of PASS when using the external anchoring question focusing on "satisfactory condition" seems to correspond to a disease activity level within the moderate range in patients with RA.<sup>8</sup> The levels of PASS for pain visual analogue scales (VAS) that have been identified across different diseases have been remarkably similar, that is, around 30–40 mm in chronic diseases (table 1) and slightly lower in acute conditions.<sup>9</sup>

Studies have also addressed the robustness of the PASS cut-off points. It appears that PASS cut-off points are stable over time,<sup>8, 11</sup> and that they are not strongly influenced by age, disease duration and gender, even if women and patients with established disease have a tendency to report satisfactory condition on levels of health status that are worse than in men or in patients with short disease duration.<sup>8</sup>

The methodology for identification of PASS may influence the identified cut-off points. It appears that the ROC approach generally provide estimates that are somewhat lower than the cut-off points identified with the 75th percentile approach.<sup>7, 8</sup>

## COMMENTS

The identified cut-off points for MCII and PASS may easily be incorporated as end points in clinical trials, and will provide information about the proportion of patients who achieve an improvement exceeding the level accepted as MCII and achieve a state accepted as PASS. Dougados *et al.*<sup>12</sup> recently validated the

external anchoring PASS question and found that it was a valid and reliable concept reflecting the patient's assessment of achieving a satisfactory health state in AS and also had discriminant capacity between active treatment versus placebo.

An emerging challenge is that new treatments have created more ambitious treatment goals than before. Inhibition of radiographic progression and achievement of remission are such goals in RA. However, PASS levels of pain VAS exceeding 30 mm may probably be considered satisfactory, but not as an ambitious accepted target of modern therapy. Further, PASS has been referred to as the value beyond which patients consider themselves well<sup>10</sup> or feel good.<sup>9</sup> However, the external anchoring PASS question is about whether or not patients consider their condition as satisfactory. We have recently shown that PASS corresponds to moderate disease activity,<sup>8</sup> which obviously is associated with a higher risk in a radiographic progression.<sup>13</sup>

In summary, MCII and PASS are useful concepts since the perspective of the patient is taken into account. Further, results from clinical studies can be expressed as proportions. The PASS concept (satisfactory condition) seems to correspond to a level of moderate disease activity (and pain VAS around 30–35 mm). Future research should identify new thresholds that also match more ambitious goals.

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