

**The variability in Minimal Clinically Important Difference and Patient Acceptable Symptomatic State values did not impact on treatment effect estimates.**

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## **ABSTRACT**

**Objective:** The Minimal Clinically Important Difference (MCID) and the Patient Acceptable Symptom State (PASS) are cut-offs dichotomising continuous values into improved or not (MCID), or in an acceptable state or not (PASS), allowing to report the success rate (proportion of patients improved or in an acceptable state) in trial arms. The objective was to investigate the influence of the choice of MCID and/or PASS values on the difference in success rate between arms.

**Study design and setting:** Analytic study. In two hypothetical trials (prespecified mean and SD for control arm score, effect sizes of 0.25 and 0.5), we calculated the success rates in control and experimental arms for different MCID and PASS values and derived the difference in success rates between arms.

**Results:** For a 0-100 score and MCID values from -40 to -10, the difference in success rate between arms ranges from 7.9% to 9.9% (ES=0.25), and from 15.9% to 19.7% (ES=0.50). For PASS values from 20 to 50, the difference in success rate between arms ranges from 7.1% to 9.9% (ES=0.25), from 15.6% to 19.7% (ES=0.50).

**Conclusion:** The MCID or PASS value has a low impact on the difference in success rate between arms in a trial.

Key words: Minimal Clinically important Difference, Patient Acceptable Symptom State, Improvement, Randomized Control Trial, Treatment Effect, Minimal Disease Activity

Running title: Low impact of MCID and PASS variability

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## **INTRODUCTION**

The Minimal Clinically Important Difference (MCID)(1-3) and the Patient Acceptable Symptom State (PASS)(4) are two concepts to help with the interpretation and communication of the results of clinical trials using patient reported outcomes measured by continuous variable (e.g. pain on a visual analogous scale - VAS). The MCID is the minimal difference representing a clinically important difference in the patient's perspective. Very close is the Minimal Clinically Important Improvement, MCII (5) that addresses only the direction of improvement, not worsening. In this paper we will use the term of MCID for these two very similar concepts. The PASS is the state beyond which patients consider their state as acceptable. Therapeutic success can thus be defined at the individual level (i.e. for each patient) as an improvement greater than the MCID, or as achieving a state acceptable at the end of the study. On a methodological point of view, MCID and PASS are then two different ways of dichotomising a continuous outcome into a binary variable of therapeutic success (the MCID being a threshold for the change in score and the PASS for the final score). At the end of the trial, they allow to report the proportion of patients benefiting from treatment (difference in proportion of improved patients or patients in an acceptable state between treatment arms). These concepts have been recognised useful (6-8), in addition to the conventional way of reporting results of trials (e.g. difference in mean change), known to be usually a more powerful approach (9-11), but not meaningful to everyone (12). MCID and PASS values have been estimated in different studies, in different diseases and in different countries (1-5, 13-20) Especially

for the concept of important improvement, a large literature exists on the Minimal Clinically Important Difference (MCID) (1). From these different estimates, to have a practical tool allowing to calculate a Number Needed to Treat, to compare studies or to pool them for a meta-analysis, for each outcome criterion, the medical community has to move towards a consensus on the MCID and PASS values for each outcome criteria so that every report would use the same cut-off values for comparison of therapeutic success. However, there is a variability among the different estimates from different studies (but estimates remain in an acceptable and clinically relevant range) and the choice of the value to be used subsequently is difficult. It should be data driven (based on the estimates) and expert based to have a good face validity. A key point in the discussion is whether the choice of the MCID and/or PASS cut-off values may have a great impact or not on the treatment effect estimates expressed as difference in success rate (proportion of patients benefiting from treatment). The aim of this study was to explore this point.

## **METHODS**

This is an analytic calculation study. The calculations were performed using pre-specified mean and standard deviation values for the distribution of the endpoint score in the control group and considering a normal distribution. We based our example on a pain endpoint assessed through a 0-100mm Visual Analogous Scale (VAS), but this can be extrapolated to any 0-100 score. The control group parameters were derived from a

cohort of 1194 patients hip or knee osteoarthritis patients treated with a nonsteroid anti-inflammatory drug during 4 weeks (21). Then, from the hypothesized effect sizes (0.25 and 0.50), we derived the mean score value in the experimental group (the SD being supposed to be the same as in the control group). For different MCID and PASS values, we calculated (from normality assumption) the success rate for the control and experimental groups as the probability of having a value (change from baseline score / final score) lower than the threshold (MCID / PASS). This then allowed to derive the difference in success rates between the control and experimental groups (i.e. the proportion of patients benefiting from treatment). We also calculated the Number needed to treat (NNT) as the inverse of the absolute success rate increase caused by treatment, i.e.  $1/\text{difference in success rate}$  (22).

For illustration purpose, we drawn figures plotting i) success rates in each group, ii) difference between these success rates as functions of the MCID or PASS thresholds and iii) derived NNT. Finally, we considered two effect sizes that can sensibly be observed (0.25 and 0.50) and made the MCID and the PASS vary across a range around relevant values according to results from previous published (4, 5, 14, 15, 17-19) and unpublished studies. The ranges we used were [-40 to -10] for MCID values, and [20 to 50] for PASS values, all for 0-100 scores. We particularly focused on the most relevant values for MCID and PASS in accordance to the OMERACT members (experts in the field of outcome criteria in rheumatology): [-15 to -25] for MCID values, and [30 to 40] for PASS values. (6)

## RESULTS

Figure 1 shows the success rates in each treatment arm, the difference in success rates as function of the MCID values and the NNT. For instance, with an effect size of 0.25, mean change in score in control group is  $-20.2$  ( $SD=24.5$ ), mean change in score in experimental group is  $-26.33$  ( $SD=24.5$ ), difference in mean score is 6.13. If the MCID value is  $-20$ , the success rate is 50.3% in the control group and 60.2% in the experimental group, thus the difference in success rates is 9.9% and the number needed to treat (NNT) is 10. For MCID values ranging from  $-40$  to  $-10$ , the difference in success rate between arms ranges from 7.9% to 9.9% (NNT from 10 to 13) if the effect size is 0.25, and from 15.9% to 19.7% (NNT from 5 to 6) if the effect size is 0.50. In the range of the most relevant values in accordance to the OMERACT members, the difference in success rate ranges from 9.4% to 9.9% (NNT from 10 to 11) if the effect size is 0.25; or 17.8% to 19.7% (NNT from 5 to 6) if the effect size is 0.50.

Figure 2 shows the success rates in each treatment arm, the difference in success rates as function of the PASS values and the NNT. For instance, if the PASS value is 30 and the effect size 0.25, the success rate is 30.7% in the control group and 40% in the experimental group, thus the difference in success rates is 9.3% and the NNT is 11. For PASS values ranging from 20 to 50, the difference in success rate between arms ranges from 7.1% to 9.9% (NNT from 10 to 14) if the effect size is 0.25, from 15.6% to 19.7% (NNT from 5 to 6) if the effect size is 0.50. In the range of the most relevant values in

accordance to the OMERACT members, the difference in success rate ranges from 9.3% to 9.9% (NNT from 10 to 11) if the effect size is 0.25 or 19.1% to 19.7% (NNT = 5) if the effect size is 0.50.

## **DISCUSSION**

This study shows that, in a range of relevant MCID and PASS values, the values chosen for MCID or PASS cut offs has a low impact on the difference in success rate between arms in a trial. In this calculation study, we assumed a normal distribution, which is reasonable for the patient-reported outcomes from our experience (data not shown). Thus our results can not be applied if an outcome criteria is not normally distributed.

No relevant difference in treatment effect estimates (assessed by the proportion of patients benefiting from treatment) was observed regardless of the cut-offs. The difference in success rate is particularly consistent in the range of the most relevant values in accordance to the OMERACT members: -15 to -25 for MCID values and 30 to 40 for PASS values. (6)

This is of help to choose, among a range of relevant values for a given endpoint, a cut off to be recommended as MCID or PASS, for use to report results of trials. However, this does not imply that any cut off can be recommended or that there is no need to agree on a single value (for each criteria) that would be use to report all trials. The aim of using MCID and PASS to report trial results in addition to the difference in mean change (which remains in general a more powerful approach) (9, 10, 23), is to provide more



meaningful information to readers not very familiar with effect size or difference in mean change. Switching from the group level to the individual level (reflecting daily practice) is not natural to most people. Thus providing the difference between arms in terms of difference in proportion of improved patients, or of patient in an acceptable state at the end of the trial is a valuable complement to the conventional way of reporting results. Furthermore, it might be an interesting tool to improve the communication of trials results to the patients, and thus to enhance shared decision making.

To achieve these goals, MCID and PASS cut-offs must have a good face validity. For instance, if PASS for pain is higher than the inclusion criteria used to be candidate to enter a study (usually 40 mm on a 0-100 VAS measuring pain), there is a problem of face validity because it would mean that we enrol patients in therapeutic trials although they are doing well. Furthermore, the message is quite different when saying that 22% and 32% of patient experienced an important improvement in control and treatment arms respectively, or if these proportions are 62% or 72% respectively. In both situations the difference in success rates between arms is 10, but the MCID is different.

We believe that these issues should be taken into account for the choice of the MCID and PASS values in the range of those estimated from studies. This choice should be expert-based, and may involve physicians, trialists and patients used to the concerned outcome criteria in monitoring their treatments. Our findings show that there is a room to take these issues into account without influencing the difference in success rate.

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Figure 1: Impact of the MCID value on the difference in success rate between arms. Mean change in pain=-20.2 in the control group; Standard deviation of the change=24.5; ES=0.25 and 0.50, respectively. In black, the success rate in each treatment group (left vertical axis). In blue, the difference in success rates, i.e. the proportion of patients benefiting from treatment (right vertical axis). In red, the NNT. In the green frame, the most relevant values of MCID in accordance to the OMERACT members.

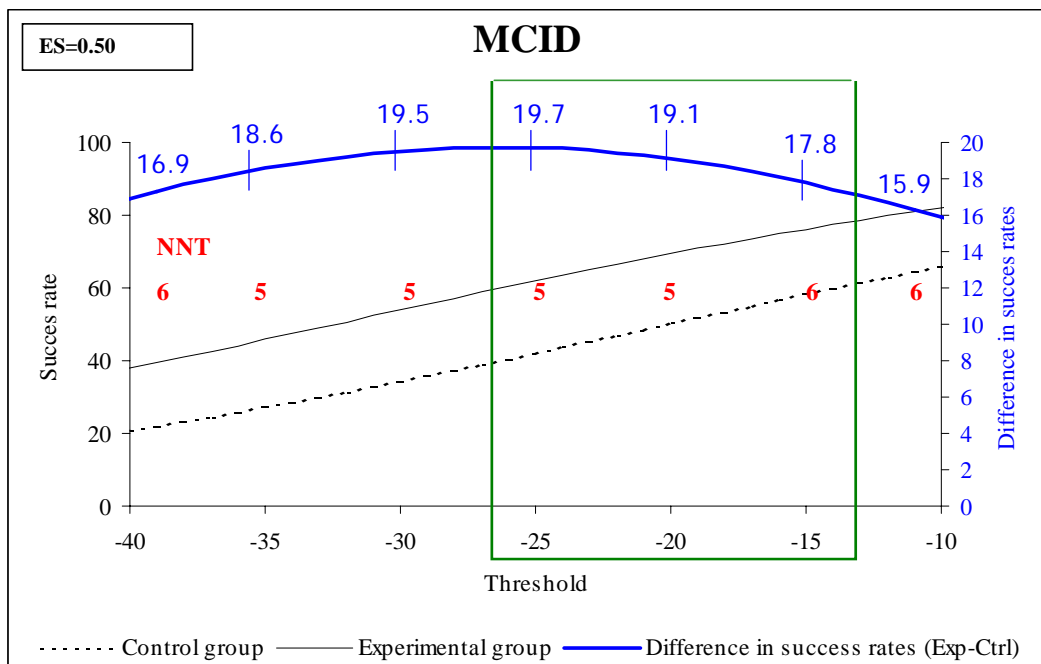
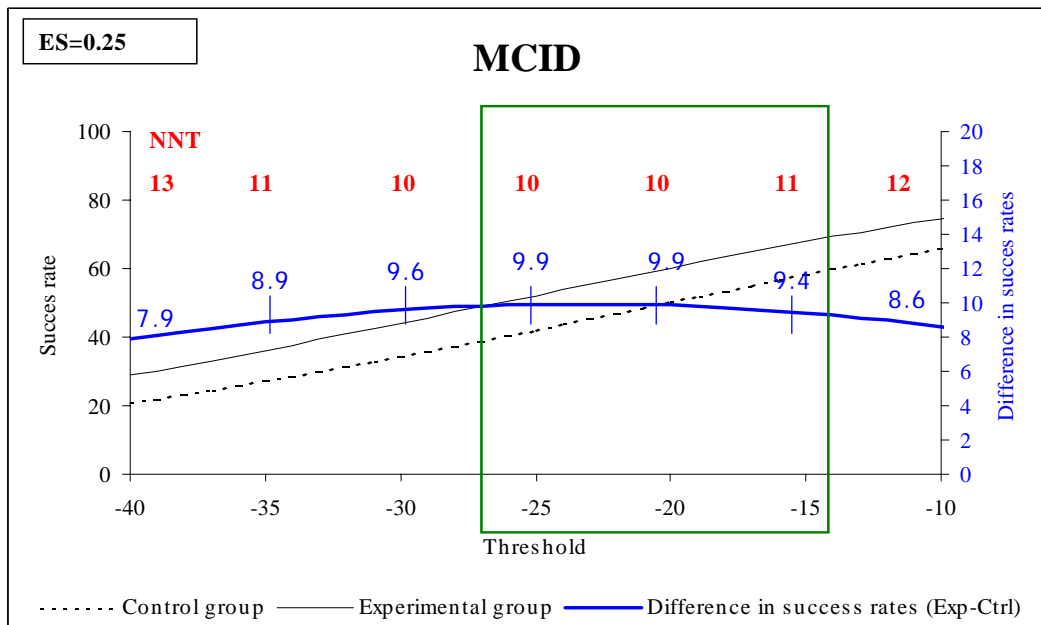


Figure 2: Impact of the variability of the PASS value on the difference in success rate between arms. Mean final pain score=41.5 in the control group; Standard deviation of the final score=22.8; ES =0.25 and 0.50, respectively. In black, the success rate in each treatment group (left vertical axis). In blue, the difference in success rates, i.e. the proportion of patients benefiting from treatment (right vertical axis). In red, the NNT. In the green frame, the most relevant values of PASS in accordance to the OMERACT members.

