

The Minimally Clinically Important Difference (MCID): What Difference Does It Make?



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Meltzer et al in their recent article, “Minimal clinically important difference (MCID) in allergic rhinitis: Agency for Healthcare Research and Quality or anchor-based thresholds?”¹ address an important issue that has serious ramifications for the allergy specialty as it discusses what constitutes an MCID for the traditional primary endpoint, total nasal symptom scores (TNSS), used in the investigation of allergic rhinitis (AR) therapeutic trials. The MCID is defined as a statistical model that attempts to define the smallest change in a treatment outcome that a patient would identify as important.¹ Three methods have traditionally been applied to calculate the MCID: (1) distribution-based methods, which relies on the spread of data using standard deviation, standard error of the mean, and effect size; (2) anchor-based methods, which compare changes in scores with an “anchor” question (eg, do you feel that you are improved by the treatment?) as a reference to determine if the patient is better after treatment compared with baseline according to the patient’s own experience; and (3) the Delphi method, which relies on a panel of experts who reach consensus regarding the MCID.¹

Historically, since 1997, the Agency for Healthcare Research and Quality (AHRQ) has been actively engaged in developing evidence-based reports relevant to clinicians and health care organizations, especially pertaining to topics that are common, expensive, and/or are significant for Medicare and Medicaid populations.² Recently, the AHRQ has targeted AR as a disease of interest. Using the Delphi approach and distribution-based methods, they proposed that a reasonable MCID for TNSS in AR clinical studies should be 30% of the maximum TNSS. Although the panel acknowledged the benefits of an anchor-based approach and the limitations of the approach they used,

they indicated that the anchor-based method could not be applied for establishing an MCID as it had not been adequately defined for rhinitis symptom scales. The authors of this current study raise justifiable concerns as the use of the AHRQ cut-point threshold value found no differences for active versus placebo AR treatments, which is in strong contrast with the experience of clinicians who treat this common condition and patients who achieve control of their rhinitis symptoms using these medications when prescribed appropriately. Thus, using too high an MCID threshold value would fail to identify effective therapies for managing AR and would also significantly stymie future drug development. In this current study, the authors have proposed an alternative approach for determining MCIDs for AR using an anchor-based threshold absolute value and have utilized validated methods for calculating distribution-based thresholds to support this approach over the AHRQ’s proposed threshold value.¹ It is important to mention that, although pharmaceutical company support was acknowledged for this study, all statistical analyses were conducted independently by the investigators in conjunction with an experienced statistical team.

Conceptually, the MCID is a very simple idea: it is the smallest change in a clinical outcome that a patient would identify as important (eg, for a patient currently on treatment A, how much better would treatment B have to work in order for the patient to be convinced to switch treatments?). In clinical practice, the MCID has limited utility because physicians do not generally view the person sitting in front of them as a generic patient, realizing that different patients have different criteria and thresholds for evaluating how well a treatment works for them. In the clinical setting, both clinician and patient are more concerned with acceptable rhinitis control than minimal important improvement. Therefore, the real value of the MCID is in clinical research. It has long been recognized that, although the *P* value is an objective measure that can be universally applied to any research setting fairly effectively, it has the very major drawback that statistical significance can be demonstrated depending on how the study was designed, even in cases where there is no clinically meaningful effect. What is particularly troublesome is that the likelihood of the occurrence of this increases with the sample size of the study so that, paradoxically, studies designed to have very low type II error (high power) are most susceptible to statistically significant, yet clinically insignificant, results. The value of the MCID is that it can be used to evaluate the clinical significance of the study results, whereas the *P* value can only be used to evaluate the statistical significance.

However, the MCID is not without limitations. This report by Meltzer et al¹ eloquently demonstrates the 2 major problems with the MCID as a criterion for evaluating clinical research. First, unlike the *P* value < .05 criteria, the MCID does not have a threshold that can universally be applied; it must be uniquely

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Conflicts of interest: J. A. Bernstein has received consultancy fees from GlaxoSmithKline, Allergy Therapeutics, Meda, and Shire; is employed by Veterans Administration Hospital, Bernstein Allergy Group and Clinical Research; has received research support from National Institute of Allergy and Infectious Diseases U44 and Shire; has received lecture fees from Shire, Baxalta, and Greer; receives royalties from Clinical Asthma Theory and Practice; and is Editor in Chief of the Journal of Asthma and Director of the Flint Hills Resources Immunosurveillance. D. T. Mauger declares that he has no relevant conflicts of interest.

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determined and validated for the specific patient population being studied. What is important for patients with severe disease might be quite different for patients with milder disease. The anchor-based approach is generally accepted to be the best approach because (1) unlike the purely statistical distribution-based approach, it takes into account the patient perspective (which is the primary intent of the MCID), and (2) unlike the Delphi approach, it is objectively evidence based. The second problem is that uniquely determining and validating the MCID for a specific patient population requires a significant amount of effort and expense. Unfortunately, this often results in an MCID that was determined for 1 population being misapplied to a different population as it is not cost effective to establish an MCID for each specific study population. An additional value of this current study is that it provides a very important and cautionary tale of the disastrous results that can follow from this sort of misapplication.

To further complicate matters, the TNSS, which is the traditional primary endpoint for most seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) studies, is not always quantified using similar scales nor are the classical symptoms of nasal congestion, nasal itching, rhinorrhea, and sneezing necessarily the most representative symptoms for all rhinitis populations. Thus, using a general cut point for the MCID developed for an SAR study may not adequately reflect clinical responses when applied to a PAR study or for future studies that may investigate more complex phenotypes like mixed rhinitis

and nonallergic rhinitis. Using an anchor-based approach to establish the MCID addresses this concern, in part, as it takes into account how well patients feel that the treatment is working based on the symptoms that are most bothersome to them.

In summary, a properly defined MCID does make a difference, especially for clinical research. Using the anchor-based approach model, the authors have demonstrated that significant MCIDs were achieved for the majority of AR studies that were otherwise reported to be negative using the MCID 30% threshold established by the AHRQ. Thus, results using the anchor-based generated MCID correlate much better with the current consensus rhinitis guideline recommendations advocated for AR treatment. In the age of evidence-based medicine, practice parameters, practice measures, and meaningful use, it is essential that assessment of clinical efficacy of a therapy reflects the clinical effectiveness experienced by the clinicians and their patients in the real world, and it appears from the study of Meltzer et al¹ that the anchor-based method for establishing an MCID is best suited for accomplishing this requirement in patients with AR.

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