EDITORIAL

Importance of minimal clinically important difference in medical research and guideline development

Manya Prasad
Department of Clinical Research and Epidemiology, Institute of Liver and Biliary Sciences, New Delhi

CORRESPONDING AUTHOR
Dr Manya Prasad, Assistant Professor, Department of Clinical Research and Epidemiology, Institute of Liver and Biliary Sciences, New Delhi - 110070
Email: manya.2311@gmail.com

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Background

P-values have posed various challenges in conducting and interpreting medical research. In an endeavor to establish more objective criteria for assessing outcomes in medical care, statistical methods have been utilized to analyze clinical trial results, often leading to a perceived dichotomy: trial outcomes are categorized as either positive or negative based on a p-value. Unfortunately, clinicians began to overly rely on the statistical significance of studies, misinterpreting their findings as clinically meaningful. Recognizing the detrimental effects of p-values, the American Statistical Association advised against their use in scientific publications (1). Instead, emphasis should be placed on the magnitude of difference between intervention and control groups. Prior to conducting a study, and in assessing the results of a body of evidence it is essential to estimate the minimum size of the difference that would be clinically significant. The smallest magnitude of benefit that patients would deem as clinically important is the minimal clinically important difference (MCID) (2). The MCID encapsulates a patient-centered approach, encompassing both the degree of improvement and the value patients attribute to this change.

Why is an MCID important?

Understanding changes in outcomes reported on a numerical scale in clinical practice should go beyond merely assessing statistical significance. It should also consider whether the observed change holds significance for patients. The significance of Minimal Clinically Important Difference (MCID) stems from its capability to gauge the genuine impact of a treatment from the patient's viewpoint. MCID functions as a tool to translate the patients' experience into measurable parameters, aligning the degree of improvement on a scale with what patients consider clinically meaningful (3).

MCID is distinct from minimally detectable difference

The minimal clinically important difference (MCID) differs from the minimal detectable difference, a term predominantly utilized in statistical literature. In statistical study design, the sample size is typically determined to be large enough to detect a change or difference from a control group that is unlikely to occur solely by random chance. The size of the study is closely associated with the likelihood of detecting a difference. Consequently, smaller

treatment effects necessitate larger sample sizes. While it is feasible to conduct a study with a substantial sample size and detect a difference between treatment and no treatment, if this difference lacks clinical significance, it is considered a minimal detectable change rather than a change of clinical importance to patients.

Relation of MCID with sample size calculation

The connection between MCID and sample size calculation involves considering how many patients are expected to undergo the minimal clinically important difference when determining the sample size for a study. This is often referred to as responder analysis. The goal is to ascertain whether a greater number of patients undergoing treatment experience this minimal important change compared to the proportion of patients in the control group experiencing the same change.

Relation of MCID with systematic reviews and guideline development

Systematic reviews and meta-analyses inform formulation of evidence-based clincal and public health guidelines. In a meta-analysis, imprecision refers to the degree of uncertainty surrounding the pooled effect estimate, often represented by confidence intervals. By comparing the width of confidence intervals in relation to the MCID, researchers can gauge whether the observed treatment effects are sufficiently precise to inform clinical decision-making. If the confidence interval crosses the threshold formed by the MCID, it suggests that the pooled effect estimate lacks precision and may not reliably reflect the true magnitude of clinical benefit or harm. Therefore, integrating MCID into the assessment of imprecision in meta-analysis enhances the interpretation of findings, guiding clinicians and policymakers in appraising the clinical significance of treatment effects across diverse populations and settings (4).

With regard to the evidence-to-decision framework, by incorporation of MCID, guideline developers can systematically evaluate the magnitude of treatment effects. This allows explicitly addressing the clinical significance of treatment effects and potential trade-offs between benefits and harms (5).

Relation of MCID with non-inferiority margins

Non-inferiority trials aim to demonstrate that a new treatment is not significantly worse than an established standard within a predetermined margin of clinical equivalence. Here, MCID serves as a vital reference point, informing the selection of an appropriate margin that reflects the smallest difference in outcomes considered meaningful by patients and clinicians alike. By aligning non-inferiority margins with MCID, researchers ensure that their conclusions accurately capture the nuanced balance between statistical significance and clinical relevance (6).

How an MCID is determined

An MCID can be derived through three main methods: consensus processes, anchor-based approaches, and distribution-based methods (7).

In the consensus method, a panel of experts independently assesses what they perceive to be a minimal clinically important difference, without knowledge of each other's evaluations. Subsequently, their scores are disclosed, allowing for reassessment and eventual consensus on the MCID as a group (Delphi method).

Anchor-based methods establish the MCID by linking changes in a numerical scale representing an outcome to an external assessment of improvement on a scale for patient important outcomes. For instance, patients may be queried about their perceived improvement after treatment, categorized as feeling "about the same," "slightly better," or "significantly better." These qualitative responses are then correlated with the numerical measurement scale utilized in the study, effectively ‘anchoring’ the numerical outcome scale to the qualitative assessment, which is presumed to hold greater significance for patients.

Distribution-based methods, on the other hand, rely solely on statistical principles, analyzing the distribution and statistical properties of scores across patients. While these methods can identify a minimal detectable effect, indicating an effect unlikely to arise from random measurement error, they lack an anchor linking numeric scores to patient-relevant assessments. Consequently, distribution-based methods may fall short in identifying significant, clinically meaningful outcomes for patients (8).

It is worth noting that in distribution-based approaches, the term MCID is sometimes replaced with "minimal detectable change," as the focus is on whether the change is substantial enough to be improbable due to chance.

Overall, while distribution-based methods have their utility in statistical analyses, they are not recommended as the primary approach for establishing MCID due to their limited ability to capture clinically relevant outcomes.

Which method of determining MCID is the best

While all three methods have their merits, the choice of method depends on the specific focus of the study. Anchor-based methods are generally preferred due to their reliance on patient experience, unlike distribution-based methods which typically lack this direct connection and thus are not recommended as the sole approach for determining MCID (7).

Each method also has its limitations. For instance, the anchor-based method's effectiveness hinges on the selection of an appropriate anchor and may be susceptible to recall bias, especially if patients are asked to recall past experiences. Consequently, the timing of such inquiries is crucial to mitigate potential biases in MCID assessment.

Ideally, determining the MCID should account for variations in different population subsets. Patients' experiences and the degree of improvement they perceive can vary significantly depending on their baseline condition. For instance, patients with more severe conditions may require a larger improvement to derive benefits compared to those with milder conditions. When designing a study, it is essential to consider the heterogeneity of the patient population and whether the treatment aims to benefit a broad spectrum of patients or a specific subset. This consideration informs study design decisions and whether separate analyses for different patient groups are warranted or if a broader approach is more suitable.

Conclusion

MCID addresses the necessity of considering not only statistical significance but also the clinical relevance of treatment outcomes, particularly in patient-reported outcome measures where interpreting changes may be complex. There are various methods for calculating the MCID. Though distribution based methods are often used, since they do not directly incorporate patient perspectives, their utility is limited. In this regard, anchor based approaches may be more suited as a primary approach. Furthermore, there is often the need for tailored approaches in determining MCID thresholds across diverse patient populations, considering variations in baseline conditions and severity levels.

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Conflict of Interest

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