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Minimal Clinically Important Difference in Randomized Clinical Trials in Ophthalmology: A Systematic Review

Jorge Monasterio-Bel

jmonasteriobel@gmail.com

Hospital Universitario de Burgos https://orcid.org/0009-0006-8841-0152

Alvaro Tello

Hospital Universitario de Burgos https://orcid.org/0000-0001-9600-7394

Sanjana Ashok

Mayret Castillo

Ester Zarzosa

Augusto Azuara-Blanco

Queen's University Belfast https://orcid.org/0000-0002-4805-9322

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Abstract

Topic: We reviewed the use of minimal clinically important difference (MCID) or related terminology, as well as the analysis of clinical relevance in ophthalmology trials, both in study design and in result reporting.

Clinical relevance: MCID is defined as “the smallest difference in any outcome of interest that patients perceive as beneficial or harmful.” It represents the minimum difference needed to consider two interventions as different or to justify a change in disease management.

Methods: We searched four databases (Medline, Embase, CENTRAL, and PubMed) from January 1, 2020, to April 15, 2024, for randomized clinical trials (RCTs) and protocols related to glaucoma, age-related macular degeneration (AMD), and diabetic retinopathy (DR). Primary outcomes were the presence of MCID or related terminology and its use in sample size estimation and result interpretation. The secondary outcome was the mention of practical importance or clinical relevance. The review followed PRISMA guidelines and was registered in PROSPERO (CRD42024536217).

Results: Sixty-four trials were included. Only three studies (4.7%), one in neovascular AMD and two in diabetic macular edema, used MCID or similar concepts for sample size calculation and interpretation. These addressed clinically significant changes in visual acuity, NEI-VFQ scores, and central subfield thickness. Nine trials (14.1%) mentioned clinical relevance or practical importance.

Conclusion: MCID is seldom used in ophthalmology RCTs. Most studies rely solely on statistical significance, which may not reflect meaningful clinical differences. Incorporating MCID in trial design can optimize sample size, improve interpretation, and enhance the clinical value of findings.

Introduction

When considering the adoption of a novel treatment, ophthalmologists need to evaluate the best available evidence and critically analyse the options available whilst also considering patients' preferences. Randomised controlled trials (RCTs) provide the foundation for evidence-based medicine and are often regarded as the gold standard for comparing the effectiveness of interventions.

Studies evaluating medical and surgical treatments report the difference in outcomes between groups of patients who receive different interventions to assess and compare their effectiveness. Outcomes are usually defined as significant only in statistical terms based on conventional hypothesis testing.

Calculating an appropriate sample size when designing a RCT is essential to reduce the risk of type I and type II errors of inferential statistics, improving the validity and power of the study, and to obtain reliable results. Additionally, a statistically significant difference might not necessarily correspond to an important difference from the clinical point of view, so clinical significance should also be considered when calculating the sample size and interpreting the results.

Researchers are thus encouraged to define the minimal clinically important difference (MCID) or minimal clinically significant difference (MCSD) for important outcomes in advance. The MCID can be defined as the smallest difference in any outcome of interest that is perceived as beneficial or harmful. [1]

Consequently, the MCID is intended to represent the smallest difference to define two interventions as similar or different or to justify a change in the management of the disease. A change greater than the MCID is considered clinically important. By applying this concept, authors can then calculate the sample size required to statistically detect the predefined MCID with appropriate confidence, avoiding wasting resources related to under- oversampling.

However, defining MCID is challenging and there can be multiple estimates for the same outcome across several factors, including the setting, health status, stage of the disease and presence of comorbidities.

MCID can be determined by several methods such as distribution-based [2], individual-focused anchor-based [3] or expert-opinion-based [4].

In this study we reviewed the use of minimal clinically important difference (MCID) and minimal clinically significant difference (MCSD) as well as the mention of practical importance or clinical relevance of findings in ophthalmological RCTs.

Materials and methods

We performed this review following the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines [5] and the protocol for this review was registered in the online database PROSPERO (CRD42024536217).

Eligibility criteria for considering studies for this review:

We included randomised controlled trials related to glaucoma of any type, and ocular hypertension (OHT); age-related macular degeneration (AMD), including neovascular (nAMD) and geographic atrophy; and diabetic retinopathy (DR), including diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR).

Only trials published from January 1, 2020, to April 15, 2024 were included. Other types of study design were excluded e.g., non-randomised comparative trials, observational studies, registry-based studies, case-control studies.

Search methods for identifying studies and study selection:

Searches were conducted with the assistance of an information specialist across four databases (Medline, Embase, Central and Pubmed) between January 1, 2020, to April 15,2024. Abstracts and titles

were reviewed by five independent investigators using COVIDENCE. A senior investigator resolved disagreements.

Data collection:
Five reviewers were involved in data extraction. A data extraction form was designed using an Excel spreadsheet. Reviewers collected the following data from each study: study title, publication date, authors, country of lead investigator, diagnostic condition, intervention, comparator, primary outcome, secondary outcome/s, sample size, duration, description of use of MCID/MCSD in the estimation of sample size, description of use of MCID/MCSD in the interpretation of the results, mention of practical importance or clinical relevance of findings and reference citation of MCID.

Risk of bias was not assessed because this review focused on the synthesis and reporting of minimal clinically significant differences in trials.

***Data synthesis and analysis*:**

We grouped studies according to ophthalmological diseases (glaucoma-OHT, AMD and DR). The primary outcomes assessed the presence of MCID or related terminology and its application in sample size estimation and interpretation of results. The secondary outcome was the mention of practical importance or clinical relevance of findings. We analysed the randomised clinical trials in which MCID and clinical relevance concept were used. We described how MCID or similar concept was defined.

Results

We identified 703 records in the databases search (see Figure, PRISMA flow diagram). After removing duplicates and screening of titles and abstracts, a total of 64 trials were included. Glaucoma and DR were the most prevalent diagnostic condition of the trials included; 26 on DR (40.63%), 26 on glaucoma (40.63%); followed by 9 on AMD (14.63%), of which 6 addressed the treatment of neovascular AMD (nAMD) and 3 focused on geographic atrophy in non-neovascular AMD, 2 on both, DR and AMD (3.13%), and 1 on glaucoma, DR and AMD (1.56%). The trials included were from 25 different countries. The most common country of lead investigator were the United States of America (USA) with 24 trials (37.50%), followed by India with 5 trials (7.81%).

Three studies (4.69%) utilised MCID or related terminology for sample size calculation and interpretation of results; these studies were from USA, United Kingdom (UK) and Israel, one of them on neovascular AMD and the other two which focused on diabetic macular edema (DME) in DR. Two studies described the use of MCID for sample size calculation based on visual acuity changes. One of these studies selected a “permitted maximal difference of 5 ETDRS letters between groups as the non-inferiority margin because a 5 ETDRS letters or less difference is not considered clinically relevant or meaningful to patients” [6, 7] and also considered the MCID in changes in central subfield thickness (CST) and in the National Eye Institute Visual Function Questionnaire (NEI-VFQ) [8–10]. The second study that used MCID for sample size calculation based on visual acuity changes chose an equivalence margin of +/-

3.5ETDRS letters at week 8 and explained that it was determined “via a meta-analysis of data from clinical trials, the minimal clinically important difference in visual acuity (5–10 ETDRS letters), that had been previously identified, [11] and advice from regulatory authorities.” [12] The third study defined the changes in CST considering that the margin chosen “approximately corresponds to CST changes exceeding 50 μm, which was shown to reflect clinically meaningful changes in a published neovascular AMD study [13, 14]”.

The practical importance or clinical relevance of differences between interventions was explicitly noted in nine trials (14.06%). Of these, 6 were focused on DR, representing 6 out of 26 trials (23.07%) of all DR-related trials. Two trials addressed nAMD (22.22%) of all AMD trials. One trial from the 26 related to glaucoma reported this concept (3.84%). Among these nine trials, five were conducted in the United States, so 5 out of 24 (20.83%) US trials considered the clinical relevance of their results. Clinical relevance of best corrected visual acuity (BCVA) results was mentioned in seven of these trials, of which diabetic retinopathy severity scale (DRSS) score is present in three of them. Clinical relevance of changes in macula on diabetic macular edema was analysed in two trials, while clinical relevance of changes in intraocular pressure (IOP), clinical importance of changes in mean subretinal fluid measurement and clinically meaningful differences between treatments in anatomical, safety, or immunogenicity was analysed once in three different trials.

Discussion

Our systematic review found that only a small minority of RCTs consider MCID in the design and interpretation of results. A statistically significant difference on its own may not be sufficient for making clinical decisions. Statistical significance is greatly influenced by the size of the study's sample. In studies with large sample sizes, even minor treatment effects, which may not be clinically relevant, can be reported as statistically significant. As a result, readers need to be cautious in assessing whether this “significance” has real clinical implications. [15]

The MCID is the smallest difference that is likely to lead to a change in management. Defining an MCID presents several challenges and can be determined by various methods.

The distribution method typically calculates a value greater than the inherent imprecision of the measurement, which is therefore likely to reflect a meaningful difference or one that can be statistically identified (e.g., minimal statistically detectable difference). [16] In distribution-based methods MCID is probably easier to define but difficult for patients and clinicians to understand and, probably, definitions should be different regarding the outcomes under consideration. [17] Furthermore, the distribution methods do not accurately capture the health changes in the participants. Expert consensus is another recognized method for determining the MCID [18].

The anchor method assesses the minimum clinically important change in score for a specific instrument. This is determined by calculating the mean change score (post minus pre) for that instrument among a group of patients for whom it is indicated. An additional measurement, the "anchor,"

is used to confirm that a minimum clinically important change (or difference) has taken place. The term "minimum" refers to the categorization of patients based on the amount of change, with the smallest change being considered "important." It is a particularly suitable method for quality-of-life measures. [16]

Most of the current literature on MCID focuses on patient-reported outcomes (PROMs), which are questionnaires that collect health outcomes directly from the people who experience them. [19] When it comes from patient-reported data, defining an MCID presents additional challenges, e.g., patients' difficulty to understand the context of improvement; retrospective assessments can be influenced by recall bias, as patients may not accurately remember the previous status of their condition. Even higher-quality clinical Practice Guidelines are unable to incorporate PROMs into recommendations because of their seldom use and limited evidence in ophthalmology [20].

Some RCTs have used MCID. For example, a MCID of approximately 5 letters on the ETDRS (Early Treatment Diabetic Retinopathy Study) scale has been established for visual acuity in patients with conditions such as DR and nAMD. [6, 7] Another instance, it has been proposed in AMD trials that changes in central macular thickness of more than 50 μm may reflect important clinical change [13].

In DME patients, differences ranging from 3.3 to 6.1 points in the overall composite scores of the NEI-VFQ-25 questionnaire have shown to be clinically significant, as demonstrated by a distribution-based method. [21] In the case of early glaucoma-related visual impairment, a change of approximately 6 points on the VFQ-25, determined using anchor-based methods, is likely to be meaningful to patients [22], although other authors have estimated a range of minimally important differences between 2.3 and 3.8 units for the NEI-VFQ and a range between 2.6 and 6.5 units for the Visual Activities Questionnaire (VAQ) in subjects with newly diagnosed open-angle glaucoma, employing anchor-based methods. [23]

A survey conducted among glaucoma specialists in the UK and an expert discussion group of the European Glaucoma Society (EGS) identified 2–3 mmHg as the MCID for IOP for comparing surgical interventions for glaucoma. Furthermore, attempts have been made to define the MCID for other non-numerical outcomes, such as differences in success rates the proportion of patients who are "drop-free" after a surgical intervention. Provided that the implementation of standardised protocols for the reintroduction of hypotensive drops during follow-up is essential for the reliability of this outcome, EGS consensus guidance have determined that the MCID for these differences in proportion of drop-free patients should be between 20 and 30% [24].

Concerning changes in global indexes of visual fields, the majority of EGS experts judged that an MCID should be not less than 2 dB between interventions. Again, the MCID should be contextualized considering factors such as the length of follow-up, the characteristics of the population being studied and the nature of the surgical intervention under investigation.

The Glaucoma Preferred Practice Pattern (PPP) Committee of the American Academy of Ophthalmology suggests using the cumulative probability of surgical success at 2 years, determined by Kaplan-Meier analysis, as the primary efficacy endpoint in MIGS trials. The suggested MCID for the cumulative

probability of surgical success is 50% for standalone MIGS and 65% for MIGS combined with cataract extraction and intraocular lens implantation (CE-IOL). The committee defines surgical success for standalone MIGS procedures as achieving an intraocular pressure (IOP) of 21 mmHg or lower, with a reduction of 20% or more from baseline, without an increase in the number of glaucoma medications, additional laser or incisional glaucoma surgeries, loss of light perception, or hypotony. The combination of CE-IOL and MIGS should offer a significant additional reduction in IOP and glaucoma medication use compared to CE-IOL alone. [25]

Conclusion

MCID is seldom used in ophthalmology trials, especially in glaucoma studies. Most published studies report results as significant solely based on statistical measures, which may not reflect an important clinical difference. Investigators are encouraged to define MCID and to describe the rationale and the methods they relied upon for its choice.

Declarations

Conflict of Interest:

The authors declare that they have no conflict of interest.

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Figures

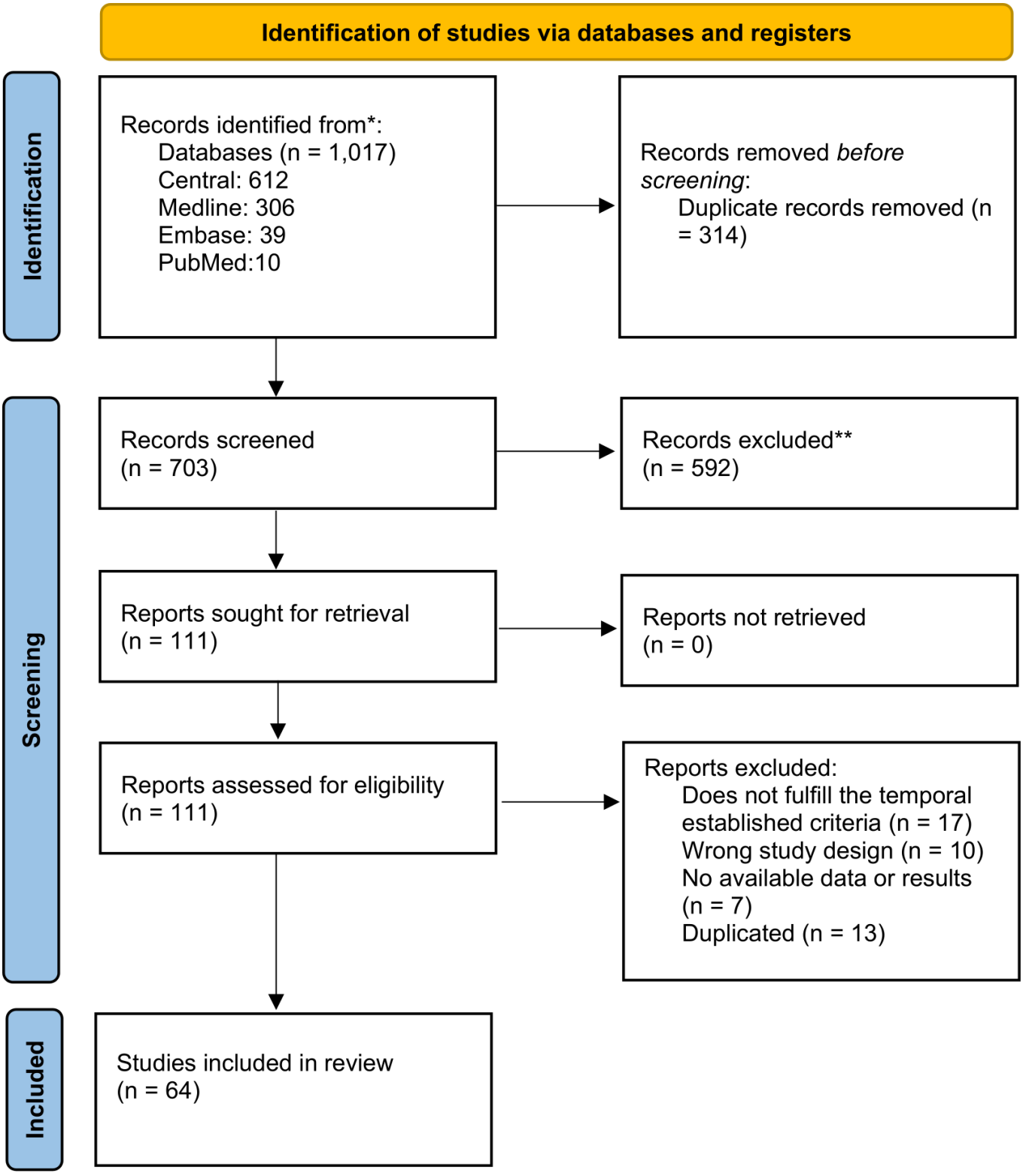


Figure 1

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

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