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Citation for final published version:

Ali, Faraz, Salek, M. S. and Finlay, Andrew 2018. Two minimal clinically important difference (2MCID): A new twist on an old concept. *Acta Dermato Venereologica* 98 (7) , pp. 715-717. 10.2340/00015555-2894

Publishers page: <http://dx.doi.org/10.2340/00015555-2894>

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2MCID (Two Minimal Clinically Important Difference): a new twist on an old conceptAli FM¹, Salek MS^{2, 3}, Finlay AY¹¹Department of Dermatology and Wound Healing, Division of Infection and Immunity, School of Medicine, College of Biomedical and Life Sciences, Cardiff University, Cardiff, UK²School of Life and Medical Sciences, University of Hertfordshire, Hatfield, UK³Institute for Medicines Development, Cardiff, UK.**Introduction**

The minimal clinical important difference (MCID) is a useful and widely used concept to interpret the meaning of health-related quality of life (HRQoL) score changes. However, in order to give a greater sense of the meaning of score change across a wider spectrum of score changes, we propose a new concept of '2MCID'. This represents a score change of twice the MCID. This approach, novel in dermatology, has been used in other areas (1, 2) and highlights therapies that reach this higher change threshold. We hypothesise that this method would better discriminate between the efficacy of interventions to help guide clinical judgment and patient progress.

HRQoL outcome measures are holistic, multi-faceted tools that capture several aspects of a patient's overall well-being (3). Such measures are increasingly being implemented in interventional studies alongside clinical objective parameters as important contributors towards morbidity and mortality data (4). Reports of studies often include HRQoL data citing statistical differences pre- and post-intervention, though statistically significant changes may not be truly reflective of meaningful change in HRQoL, particularly within large sample sizes which may produce statistically significant change despite the change being small. (5)

The MCID is described as the minimum difference needed for a patient to perceive the change as beneficial (6) and may be used to determine whether a medical intervention improves patient perceived outcomes. Factors to consider when calculating the MCID for a particular outcome include: patient baseline severity, particular disease or condition, patient demographics and treatment. As a result, there is no consensus on the best methodology for calculating the MCID (7), and values may therefore differ within the same population. Despite these limitations, it is still considered more useful for clinicians to assess the effectiveness of an intervention based on the patient's perspective, rather than solely on statistical significance.

Our recent systematic review demonstrated that the most commonly utilized QoL tool in dermatological trials is the Dermatology Life Quality Index (DLQI), with an MCID of 4 points (8, 9). While carrying out this systematic review it appeared that multiple MCID could provide a further aid to the interpretation of the results and we felt that this novel concept deserved further exploration. We have therefore applied the concept of 2MCID to data summarized in that review (8).

Methods

A systematic review was presented by Ali et al (8). We have introduced the concept of 2MCID to that dataset (i.e. DLQI score change of at least 8) to demonstrate comparative efficacy between interventions.

Results

A total of 100 trials were identified by the systematic review, covering a diverse range of interventions. As the DLQI was the most commonly used QoL measure (83% of studies), the

2MCID concept was tested on interventions with documented DLQI scores. Figure 1 summarises all the interventions that met the different MCID thresholds.

For topical treatments, clobetasol 0.05% spray showed the greatest improvement at 4 weeks (2MCID, 8 point improvement), followed by calcipotriol plus betamethasone at 8 weeks (6.4 points). These changes are comparable to ustekinumab 90 mg at 12 weeks (average 2MCID (8 point improvement) and ciclosporin 3-5 mg/kg at 12 weeks (6.6 point improvement). No other topical therapy reached 2MCID. However, it is important to consider the context of baseline psoriasis severity, treatment duration and long-term QoL maintenance.

Methotrexate 15 mg at 16 weeks was the only systemic intervention over the 2MCID threshold (8.7 points). This was comparable to several biologics, including etanercept 50 mg at 24 weeks and ustekinumab 90 mg at 12 weeks (8.7 points).

Infliximab 5 mg/kg at 16 weeks and secukinumab 300 mg at 12 weeks on average demonstrated the largest improvement in DLQI score of 11.4 (>2MCID), just short of 3MCID. Amongst other interventions, an energy-restricted diet with immunosuppressive therapy at 24 weeks recorded DLQI improvement of 14.4 (3MCID). DLQI at 12 weeks improved by 11.2 (>2MCID) with PUVAsoL 0.6 mg/kg + isotretinoin 0.5 mg/kg: for PUVAsoL alone, DLQI improvement was 6.8.

For studies with treatment endpoint and assessment at 12 weeks, the interventions with the greatest average DLQI impact in each category were secukinumab 300 mg (2MCID, 11.4 points), ciclosporin 3-5 mg/kg (1MCID, 6.6 points), PUVAsoL 0.6 mg/kg + isotretinoin 0.5 mg/kg (2MCID, 11.2 points), Liquor Carbonis Distillate solution 15% (1MCID, 5.8 points) and educational programme (1MCID, 4 points).

Discussion

Previously, Leaf and Goldfarb (1) described the impact of erythropoiesis stimulating agents (ESAs) on HRQoL using Short-Form 36 (SF-36) and The Kidney Disease Questionnaire (KDQ). However, the authors only infrequently and arbitrarily refer to score changes for these measures using multiples of MCID without formal utilization of the concept. Similarly, Jones, Gelhorn (2) equate a change of 'twice the MCID' to a 'large benefit' when comparing active treatments for COPD against placebo using the St. George's Respiratory Questionnaire (SGRQ). However, neither study formally explored or stratified results using this concept.

Although it is possible to apply score banding descriptors (10) to describe the number of patients within each score band pre and post intervention, there needs to be a method that can discriminate between the extent of the effect of interventions on QoL. The concept of 'multiple-MCID' could add meaning to score change when comparing therapies, and possibly when comparing results across different QoL instruments as a 'unit of change'. The question may arise as to why 2MCID should be chosen rather than other multiples. 2MCID appears to be a practical threshold providing the potential of a meaningful 'hurdle' that developers of new interventions might strive to achieve. As indicated in the analysis of the systematic review, only one out of a hundred RCTs demonstrated a change of 3MCID indicating that a 3MCID 'hurdle' would be a difficult and impractical threshold to achieve.

This 'pilot study' of the concept of 'multiple-MCID' demonstrates the potential benefit of comparing the extent of impact of different categories of interventions on QoL and interpreting change over time. For example, we have demonstrated that certain systemic interventions may impact QoL to the same extent as certain biologic treatments. Similarly, certain topical treatments may be as efficacious as systemic alternatives. Interpretation of these conclusions, however, should take into account that the dataset of the systematic review is not homogenous and often patients have

different baseline severities. Furthermore, although MCID values are applied across a spectrum of scores in interpreting change in scores of a measure, in reality the MCID score value may be different depending on whether the score change is at the lower or upper end of a HRQoL measure score range. This criticism of the concept of MCID requires further investigation. One way to explore this would be through meta-regression where the magnitude of effect on DLQI is regressed on baseline severity. The concept of 2MCID may be too simplistic: ideally the identification and calculation of a multiple-MCID score should be based on prospective research that takes into account patient assessment of a higher level of change, using an anchor question based on, say, "Major clinically important difference".

Despite these reservations and investigation suggestions, as a 'proof of concept' we believe 'multiple-MCID' provides additional meaningful information on clinical improvement and may be of value to clinicians, patients and the pharmaceutical industry. For example, medications that meet the '2MCID' minimum threshold might be more easily approved by both pharmaceutical regulatory authorities and health technology assessment (HTA) agencies. This concept may also enable researchers to distinguish more efficiently between interventions and comparators in trials, potentially improving patients' access to the most effective new medicines. Prospective longitudinal studies could aim to prove the usefulness of the concept before implementing it on a broader scale. Further work is required before this novel concept is adopted in treatment decision-making and in reimbursement appraisals.

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Figure 1 Mean DLQI score change in 100 clinical trials for psoriasis (8), showing those interventions that reached 1 MCID and 2 MCID score change.

