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Meaningful benefit and minimal clinically important difference (MCID) in Alzheimer's disease: Open peer commentary

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Abstract

Introduction: Approval of the anti-amyloid monoclonal antibodies has stimulated an important discussion of the value to be placed on the magnitude of slowing achieved by treatment compared to placebo.

Methods: The minimal clinically important difference (MCID) was reviewed in the context of other measures and analyses that provide perspective on the meaningfulness of treatment responses.

Results: TheMCID is a clinician-anchored approach to making this determination. The MCID applies best to symptomatic therapies for which the drug–placebo difference remains constant. Disease-modifying therapies produce a progressive divergence of drug and placebo trajectories; early in the course the MCID would not be achieved, later the MCID will be achieved, and with continuing therapy the MCID will be exceeded. Clinicians are not the only stakeholders involved in determining the value proposition of slowing disease progression. Patient-reported outcomes and caregiver-related measures offer important complementary insights. Analytic approaches also widen the perspective on the observed drug–placebo differences. Risk ratios, numbers needed to treat versus number needed to harm, time-to-event analyses, and predictive benefits based on biomarkers all add depth to the discussion.

Discussion: Multiple stakeholder perspectives are needed to determine the importance to be attributed to the therapeutic changes observed with monoclonal antibody therapies and other emerging treatments.

Anti-amyloid monoclonal antibodies (mABs) slow the clinical deterioration of patients with early Alzheimer's disease (AD) confirmed by amyloid studies. The Phase 2 and Phase 3 studies of donanemab, the Phase 2 and Phase 3 clinical trials of lecanemab, and the EMERGE clinical trial of aducanumab demonstrated slowing of the progression of AD on composite outcomes by 25% to 40% depending on the measure used.[1–4] Slowing of clinical decline has been shown on both cognitive instruments and functional tools in addition to the primary composite outcomes. Two of these agents, aducanumab and lecanemab, have received accelerated approval from the US Food and Drug Administration (FDA), and lecanemab has been granted standard approval. The clinical outcomes are supported by biomarker changes including marked amyloid plaque lowering demonstrated by amyloid positron emission tomography (PET) and effects on downstream biomarkers including phospho-tau (p-tau) 181, p-tau 217, and glial fibrillary acidic protein (GFAP).[1–3,5]

The outcomes of these trials have stimulated a robust and important discussion on the magnitude of the changes observed and whether they are sufficient to warrant the substantial demands on patients that treatment with mABs makes and the reimbursement of the cost

of therapy from the public purse. The magnitude and importance of the drug–placebo difference observed is dependent on the measurement instrument involved, the analytic approach adopted, and the audience to whom the value proposition is addressed. The minimal clinically important difference (MCID) is one way of determining if a clinician believes that a certain clinical threshold has been achieved. Andrews et al. in their original publication and in their recent commentary present the clinician-anchored MCID measure for the Clinical Dementia Rating–Sum of Boxes (CDR-SB) as residing between a difference of 1.19 described as clinically meaningful and 0.02 described as no meaningful difference.[6,7] For individuals with cognitive change only (e.g., no behavior or functional changes, like those included in mAB trials), the MCID for the CDR-SB ranged from 0.74 (meaningful difference) to 0 (no meaningful difference). There was no intervention in the study reported, and the MCID refers to the change observed in participants with progressive disease beginning at different levels of impairment (normal, mild cognitive impairment [MCI]-AD, mild AD dementia, moderate to severe AD dementia) considered meaningfully different since the patient's last visit. The diagnoses of the patients from whom the data were collected were determined based on clinical measures and diagnostic criteria without confirmation of amyloid status, creating a population different from that included in early AD trials of mABs. In the study of lecanemab, both the placebo group and the active treatment group had CDR-SB declines from baseline that exceeded this MCID, 1.66 in the placebo group versus 1.21 in the group treated with lecanemab, a difference of 0.45 or a 27% reduction in decline for those on treatment compared to those on placebo.[3] The drug–placebo difference did not meet the boundary of definite MCID and exceeded the boundary of no MCID established by Andrews et al. The US FDA has not provided guidance regarding the potential application of MCID to trial outcome interpretation and no specific MCID is required for drug approval.[8]

The MCID established by Andrews et al.[6] used an anchor mechanism dependent on clinician judgment. For clinicians, MCID depends on the observed change from the last assessment. The experience of the clinician, the thoroughness of the examination, and the strategy used for determining meaningful change all influence the outcome of this strategy.[8] Clinicians have an important perspective on minimal change, but they are not the only stakeholders in the discussion, and they may not be the most sensitive observers. In a 48-week trial of donepezil in patients with MCI, Doody et al. found no drug–placebo difference on the CDR-SB but observed statistically significant differences in favor of treatment on the Perceived Deficits Questionnaire and the Patient Global Assessment, scales more closely linked to patient experience and caregiver observation.[9] The patient and care partner view of change is a key aspect of the dialogue on meaningful benefit.

The MCID is most applicable to symptomatic therapies for which the drug–placebo difference remains stable after the initial therapeutic response. With disease-modifying therapies such as the mABs, one sees an increasing drug–placebo difference during the trial, and this divergence continues at the arbitrary end of the trial at 18 months. This suggests that the MCID would not be met in the early part of a trial when there is little separation between drug and placebo, could be met later in the exposure as drug–placebo differences increase, and would be exceeded as treatment/no treatment differences continue to expand (Figure 1). The gradual accrual of brain pathology even while slowing the course of the disease is likely to eventually overwhelm treatment effects, but there was no suggestion of a waning of treatment benefit at the end of the current trials.[1–3,10] The anticipated increasing drug–placebo difference observed in trials of disease-modifying agents is the foundation for the concept of cumulative benefit as an outcome derived from disease modification.[11]

RESEARCH IN CONTEXT

1. **Systemic review**: The emergence of anti-amyloid monoclonal antibodies as disease-modifying therapies for patients with early Alzheimer's disease (AD) requires examination of the value to be attributed to the slowing of decline observed in clinical trials.
2. **Interpretation**: The minimal clinically important difference (MCID) is one means of assessing the importance of the magnitude of the drug–placebo difference achieved in a clinical trial. The MCID should be complemented by other types of analysis that represent the perspectives of other important stakeholders.
3. **Future directions**: Progress in developing new therapies for AD requires consideration of how best to analyze and weigh the importance of the magnitude of effects observed in a trial. The analytic framework for determining meaningful benefit is evolving.

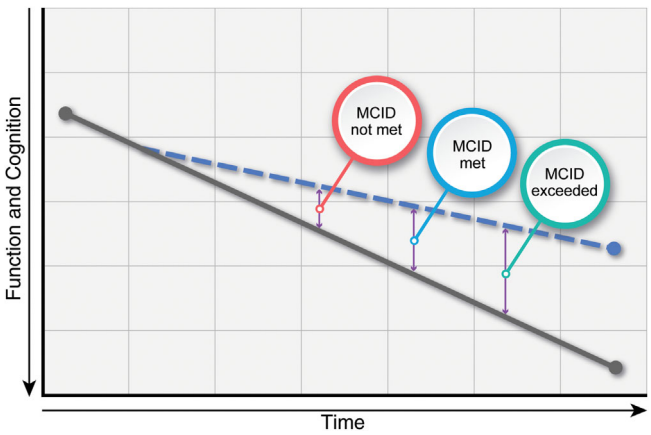

FIGURE 1 Illustration of hypothetical Alzheimer's disease clinical decline over time and an intervention that slows the progression by disease modification. The minimal clinically important difference (MCID) would not be met early in the treatment period when little treatment effect has occurred and would be expected to meet and exceed the MCID as the impact of therapy increases over time

There are several important ways of measuring the benefit of treatment.[11] The FDA has stated that benefit on cognitive measures by itself is meaningful, especially in the early phases of AD.[12] Functional and behavioral measures are highly regarded as treatment outcomes for patients, care partners, and practitioners. Patient (or care partner) reported outcomes are essential in trials as part of our evolution toward more patient-centered studies and care. Care partner measures such as quality of life, hours devoted to care, and stress associated with care represent other important perspectives on desirable treatment outcomes from therapeutic interventions. Socioeconomic and health outcome measures provide key information on the economic impact of treatments such as fewer emergency room visits, fewer out-of-pocket expenses for ancillary services, delay to nursing home placement, and gain in quality-adjusted life years (QALYs) as benefits of treatment.[13] Analytic approaches assist in exploring the importance of the magnitude of change observed in standard data collection circumstances such as trials. Standardized effect sizes allow comparison among agents. Risk ratios and odds ratios are types of responder analyses that provide insight into trial outcomes. Numbers needed to treat (NNT) and numbers needed to harm (NNH) analyses are often useful for developing economic perspectives on data. MCID fits into this repertoire of analytic tools that can help interpret trial data. MCID is subject to several types of analyses including non-inferiority approaches that assist in interpretation.[14] Time-to-event analyses applied to trial data facilitate understanding how much an intervention delays the occurrence of pre-specified events or thresholds in treatment arms compared to placebo arms of a trial. A delay of loss of function may be easier to grasp than a score difference and provides a useful means of communication of treatment effects.[15] Recent analyses suggest that the magnitude of effect observed in mAB trials translates into approximately 3 to 5.3 months of delay in the course of an 18-month trial.[16,17]

Identifying and quantitating meaningful benefit in preclinical trials in which participants have no symptoms and clinical benefit cannot be measured is challenging. Concepts such as cumulative benefit recognize the increasing drug–placebo difference in subtle neuropsychological deficits or delaying time to onset of neuropsychological impairment offer two means of measuring treatment benefit in trials initiated in asymptomatic phases of AD.[18,19] Accelerated approval based on reduction of plaque amyloid on PET imaging sets the stage for consideration of predictive benefit based on amyloid plaque removal during asymptomatic periods of AD as the basis for assessing meaningful benefit.[20] Increasing confidence in other biomarkers may create additional options for predictive benefit determination.

Single-measure approaches provide valuable but limited insight into therapeutic responses. Considering a repertoire of outcome measures and analytic strategies for assessing meaningfulness allows a comprehensive multi-stakeholder evaluation of the benefit of emerging treatments for AD.

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CONFLICT OF INTEREST STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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