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LETTER

Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials

The article entitled "Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials" was published in 2019 by Andrews et al. in *Alzheimer's & Dementia*.[1] This study has emerged as perhaps the most influential investigation on the subject of minimal clinically important differences (MCID) in the key outcome measures used in therapeutic trials for Alzheimer's disease (AD). For example, Liu et al. used its results as the benchmarks against which they compared effect sizes for a range of AD trials: "for mild cognitive impairment (MCI) and mild Alzheimer's disease, differences of 0.98 and 1.63 points for clinical dementia rating scale sum of boxes (CDR-SB)… represented clinically meaningful change."[2] More recently, in an editorial by Walsh et al., the same statistics were used to dismiss the clinical meaningfulness of the Clarity AD lecanemab results,[3] which included therapeutic differences in CDR-SB of 0.35 and 0.62 in mild cognitive impairment (MCI) and mild Alzheimer's disease (AD) dementia, respectively.[4]

However, a close reading of the report of Andrews et al. reveals that its primary analyses are based on an erroneous assumption that renders its central results invalid.[1] The authors estimated MCID for clinical outcomes using an anchor-based approach (clinician's assessment of meaningful decline). The study utilized the publicly available Uniform Data Set (UDS) from the National Alzheimer's Coordinating Center (NACC), which comprises data from 35 past and present Alzheimer's Disease Centers supported by the National Institute on Aging.[5]

The authors' anchor-based analyses assume incorrectly that the clinician is evaluating decline relative to the previous visit. In fact, Question 3a in the relevant NACC UDS form (uds2-fvp-b9) asks "Relative to previously attained abilities: Does the clinician believe there has been a current meaningful decline in the subject's memory, non-memory cognitive abilities, behavior, or ability to manage his/her affairs, or have there been motor/movement changes?" The question is intended to differentiate an acquired cognitive disorder from lifelong impairment, for example, due to an intellectual developmental disorder. The clinician's assessment is, therefore, not concurrent with the measured changes in CDR-SB, and other clinical instruments, since the most recent visit.

This faulty premise leads to the result that the vast majority of patients with MCI and nearly all with dementia are believed to exhibit meaningful decline at every visit: "When evaluated by disease severity, the proportions of visits with clinically meaningful decline increased with increase in disease severity: 16% of visits in the 'normal' cohort had clinically meaningful decline compared with 82% of visits in the MCI-AD cohort, 97% in the mild AD dementia cohort, and 99% visits in the moderate-severe AD dementia cohort."[1] It also leads to the conclusion that virtually all between-visit changes in CDR-SB and other instruments represent clinically important differences, and yields faulty estimates of MCID. In addition to the anchor-based analyses, the authors also include distribution-based methods. However, as they note, such analyses alone do not reference the clinical context, and are not generally recommended in the absence of anchor-based approaches.[1,6]

Apart from this flawed assumption, a related problem with the analysis of Andrews et al. is that determination of meaningful decline is driven by the duration of the follow-up period in the NACC UDS (1 year). Because most participant visits in these categories are classified as showing meaningful decline, the CDR-SB values associated with this decline largely reflect the observed decline in this measure over 1 year: 0.98 in MCI and 1.63 in mild AD dementia.[1] For example, if the follow-up period were instead 18 months, then declines of ≈50% more might be indicative of meaningful decline. In comparison, in the Clarity AD study of lecanemab (61.5% of participants with MCI, 38.5% with mild AD dementia), the placebo group showed a decline of 1.66 points in the CDR-SB over 18 months.[3] By this standard then, a therapeutic agent would essentially need to halt progression to have a clinically meaningful effect.

The authors should be commended for clarifying recently that their study was intended only to identify thresholds of meaningful within-patient progression and should not be used for determining meaningful group-level differences in clinical trials.[7] However, they should still acknowledge their error, as it pertains to estimating meaningful within-patient decline.

If longitudinal cohorts are to be utilized for evaluating clinically meaningful differences in the CDR-SB and other instruments used

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in AD trials, then—at a minimum—these should include dedicated judgments of clinically meaningful change that are fully independent of the specific instruments being evaluated, and they should also include shorter follow-up periods to establish the threshold of minimal differences.

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CONSENT STATEMENT

Consent was not necessary, since no human subjects were used for this letter to the editor.

Christopher H. Van Dyck
Ryan S. O'Dell
Adam P. Mecca

Department of Psychiatry, Alzheimer's Disease Research Unit, Yale School of Medicine, New Haven, Connecticut, USA

Correspondence
Christopher H. van Dyck, Alzheimer's Disease Research Unit, Yale University School of Medicine, One Church Street, 8th Floor, New Haven, CT 06510, USA.
Email: christopher.vandyck@yale.edu

REFERENCES

1. Andrews JS, Desai U, Kirson NY, Zichlin ML, Ball DE, Matthews BR. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. *Alzheimers Dement (N Y)*. 2019;5:354-363.
2. Liu KY, Schneider LS, Howard R. The need to show minimum clinically important differences in Alzheimer's disease trials. *Lancet Psychiatry*. 2021;8(11):1013-1016. doi:10.1016/S2215-0366(21)00197-8
3. Van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab for treatment of early Alzheimer's disease. *N Engl J Med*. 2023;388(1):9-21. doi:10.1056/NEJMoa2212948
4. Walsh S, Merrick R, Richard E, Nurock S, Brayne C. Lecanemab for Alzheimer's disease. *BMJ*. 2022;379:o3010. doi:10.1136/bmj.o3010
5. Information and Resources. NACC researcher home page, National Alzheimers Coordinating Center. University of Washington. https://www.alz.washington.edu/WEB/researcher_home.html
6. Leidy NK, Wyrwich KW. Bridging the gap: using triangulation methodology to estimate minimal clinically important differences (MCIDs). *COPD*. 2005;2(1):157-165. doi:10.1081/copd-200050508
7. Petersen RC, Aisen PS, Andrews JS, et al. Expectations and clinical meaningfulness of randomized controlled trials. *Alzheimers Dement*. 2023 Feb 7. doi:10.1002/alz.12959. Online ahead of print.

SUPPORTING INFORMATION

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