Received: 8 August 2024 | Revised: 13 September 2024 | Accepted: 23 November 2024

DOI: 10.1002/trc2.70032

Alzheimer's & Dementia
Translational Research & Clinical Interventions

OPEN PEER COMMENTARY

The problem of multiple adjustments in the assessment of minimal clinically important differences

Fabricio Ferreira de Oliveira

Escola Paulista de Medicina, Federal University of São Paulo (UNIFESP), São Paulo, Brazil

Correspondence
Fabricio Ferreira de Oliveira, Escola Paulista, de Medicina, Universidade Federal de São Paulo (UNIFESP), Rua Botucatu 740, Vila Clementino, CEP 04023-900, São Paulo, SP 04552-060, Brazil.
Email: fabricioferreiradeoliveira@hotmail.com

Abstract

INTRODUCTION: Anthropometric, demographic, genetic, and clinical features may affect cognitive, behavioral, and functional decline, while clinical trials seldom consider minimal clinically important differences (MCIDs) in their analyses.

METHODS: MCIDs were reviewed taking into account features that may affect cognitive, behavioral, or functional decline in clinical trials of new disease-modifying therapies.

RESULTS: The higher the number of comparisons of different confounders in statistical analyses, the lower *P* values will be significant. Proper selection of confounders is crucial to accurately assess MCIDs without compromising statistical significance.

DISCUSSION: Statistical adjustment of the significance of MCIDs according to multiple comparisons is essential for the generalizability of research results. Wider inclusion of confounding variables in the statistics may help bring trial results closer to real-world conditions and improve the prediction of the efficacy of new disease-modifying therapies, though such factors must be carefully selected not to compromise the statistical significance of the analyses.

KEYWORDS
activities of daily living, risk factors, behavioral symptoms, cognitive disorders, dementia, neurodegenerative diseases, neuropsychiatry

Highlights

- Anthropometric, demographic, and clinical features may affect cognitive, behavioral, and functional decline.
- Clinical trials seldom take minimal clinically important differences (MCIDs) or their confounders into account.
- Generalizability of research results requires the assessment of multiple confounding factors.
- The higher the number of comparisons involved, the lower *P* values will be considered significant.
- Use of MCIDs adjusted for confounding factors should be implemented when outcomes are not susceptible to translation into absolute benefits.

Minimal clinically important differences (MCIDs) are the smallest changes on an outcome measure that are clinically significant to add benefit to the life of a patient or to be seen as meaningful for caregivers or health-care providers.[1] They quantify changes in disease manifestations that do not rely on statistical significance alone and, when it comes to dementia, they vary according to each disease stage[2] and to the number of individuals who serve as "anchors" to evaluate such differences.[3]

A recent systematic review[1] identified the MCIDs in each stage of Alzheimer's disease (AD):

1. In mild cognitive impairment, meaningful changes would be +2 to +3 points on the Alzheimer's Disease Assessment Scale Cognitive subscale (ADAS-Cog), +1 point on the Clinical Dementia Rating Sum of Boxes (CDR-SB), −5 points on the integrated Alzheimer's Disease Rating Scale, or −1 to −2 points on the Mini-Mental State Examination (MMSE).
2. In mild AD, meaningful changes would be +3 points on the ADAS-Cog, +2 points on the CDR-SB, −9 points on the integrated Alzheimer's Disease Rating Scale, or −2 points on the MMSE.
3. In moderate to severe AD, meaningful changes would be +2 points on the CDR-SB or a change of −1 to −3 points on the MMSE.

MCIDs are essential to determine sample sizes and trial durations based on outcome measures of interest. Clinically significant outcome measures include cognitive status, functional improvement, quality of life, mood, and caregiver burden. MCIDs that are not achieved early may be exceeded with ongoing treatment given the fact that disease-modifying therapies produce a progressive divergence of drug and placebo trajectories.[4] Nevertheless, assessment of such differences may be challenging in conditions when patients are unable to communicate the way they feel about their treatment, such as in aphasic syndromes.[5]

Translation of research results into the real world requires the assessment of multiple confounding factors that may affect such results. The larger the number of inferences made, the more likely there are to be erroneous findings. Statistical adjustments for multiple comparisons are critical, and a quality issue of the study design, not just a formatting suggestion of limited importance.

Different features that may affect cognitive, behavioral, or functional decline in clinical trials of new disease-modifying therapies include, but are not restricted to:[6] sex, age at disease onset (or current disease stage), body mass index, waist circumference, visual and hearing acuity, education, diet, drug therapy, mood disorders, lifetime sanitary conditions, lifetime occupational complexity, lifetime engagement in cognitive and physical activities, cerebrovascular risk factors (combined or in isolation), use of a pacemaker, creatinine clearance, history of head traumas with unconsciousness, history of treated systemic bacterial infections, previous surgical procedures under general anesthesia, and genetic variants. Some of these features may be hard to quantify, such as cognitive and physical activities, with questionable power to discriminate the engagement of different patients and their effects. However, the impact of most of these features is unquestionable, given the fact that the prevalence of multiple comorbid proteinopathies and cerebrovascular disease increase with age, accounting for > 50% of the variance in cognitive outcomes,[7] and leading to potentially lower benefits of disease-modifying therapies for older patients.

The full spectrum of genetic variants that may affect the results of clinical trials is hard to assess. However, restricting the search to a few variants of relevance is essential for any study assessing MCIDs. Among these, the most traditional ones would be apolipoprotein E (*APOE*) alleles (ε4, ε3, ε2, and the rare ε3r).[8] *APOE* ε4 carrier status is known to affect the results of studies with patients who have Lewy body dementia syndromes,[9] vascular cognitive impairment and dementia,[10] and, most importantly, disease susceptibility, age at onset, and behavioral features of late-onset AD.[11] *APOE* ε4 carrier status also mediates the harmful prospective effects of second-generation antipsychotics and antiepileptic drugs on cognitive and functional changes in these patients.[8] In addition, *APOE* ε4 carrier status seems to wield a non-linear effect on cognitive and functional decline in late-onset AD and is a major genetic risk factor for faster brain atrophy, blood–brain barrier dysfunction, inefficient neural repair, cerebral amyloid beta (Aβ) deposition, and dissemination of neurofibrillary tangles,[11] as well as for the development of amyloid-related imaging abnormalities (ARIAs; including ARIA-E and ARIA-H) in patients using anti-Aβ immunoglobulin G (IgG)1 monoclonal antibodies.[10]

The significance of all research results must be adjusted according to the comparisons conducted on the variables involved. The higher the number of confounding factors involved, the closer we are going to be

RESEARCH IN CONTEXT

1. **Systematic review**: The literature was reviewed by way of articles found on PubMed. While most clinical trials (gold standards for approval of new therapies) use stringent eligibility criteria to reduce the heterogeneity of the participants, the generalizability of the findings may be compromised due to negligence of minimal clinically important differences (MCIDs) and all anthropometric, demographic, and clinical features that may affect cognitive, behavioral, and functional decline, thus diverting them from real-world conditions.
2. **Interpretation**: Consideration of all confounding factors that may affect MCIDs in clinical trials increases external validity, though multiple adjustments according to the number of comparisons involved require lower *P* values to be considered significant.
3. **Future directions**: The inclusion of multiple confounding factors in the statistics of MCIDs in clinical trials should be widely implemented to bring their results closer to real-world conditions and improve prediction of the efficacy of new therapies.

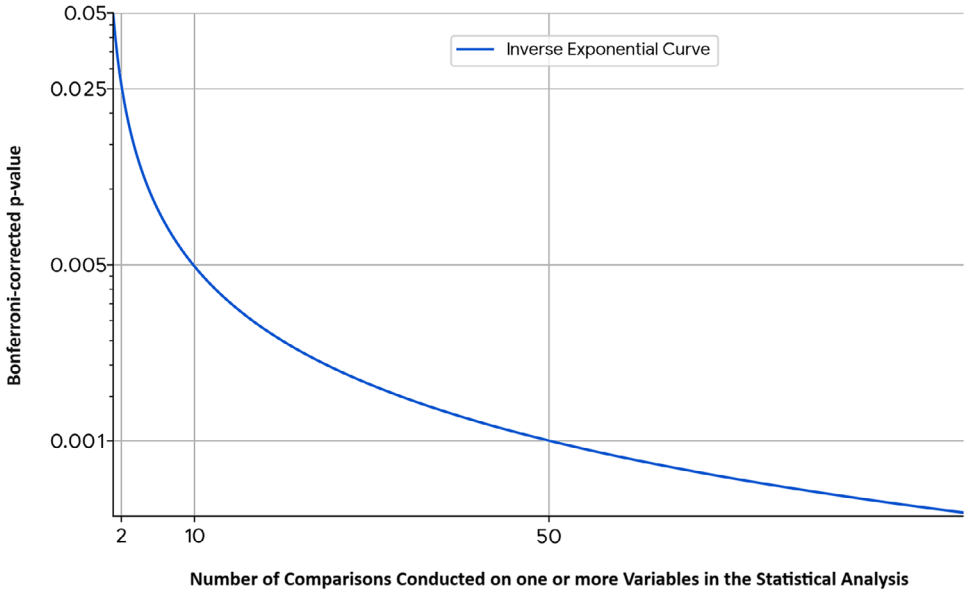

FIGURE 1 Graphical representation of Bonferroni corrections to *P* values as a strategy to adjust the total α error to the number of comparisons involving hypothesis-driven variables. While countless confounders may affect the translation of research results into the real world, statistical adjustments for multiple comparisons are critical to ascertain the quality of the analyses

to the real world, though leading to lower *P* values to be considered significant if multiple comparisons are conducted (see Figure 1). Proper selection of such confounding factors is essential to accurately assess MCIDs without compromising statistical significance. Clinical trials usually use harmonized assessments, randomization (making patient groups comparable among them in the distribution of confounding factors), and stringent eligibility criteria to reduce clinical and biological heterogeneity of the targeted disorder,[12] though such strategy may often reduce the generalizability of the findings by deviating them from real-world conditions.

Historically, AD has been treated with exercise and cognitive and behavioral therapies, with limited results.[13] Symptomatic therapies may be synergistic and offer relief,[14] but do not prolong survival or considerably change the disease course beyond the moderate dementia stage.[15] The advent of anti-Aβ IgG1 monoclonal antibodies (lecanemab, donanemab, and the now off-market aducanumab), as novel immunotherapies offered some hope, but severe side effects along with limited benefits[16] precluded widespread use: estimates are that < 10% of patients with early AD are eligible to receive them, after consideration of inclusion and exclusion criteria.[13] The trials of lecanemab and donanemab showed high effectiveness for the removal of brain Aβ but only modest effects on the reduction of cognitive and functional decline compared to placebo;[4] furthermore, these effects did not reach MCID thresholds.[16] In addition, the trials that validated these drugs did not take many confounding factors into account in the statistics, thus deviating them further from real-world conditions.

The risk/benefit ratio of high-clearance immunotherapies in early AD is so far questionable based on clinical trial results. Donanemab therapy did not show a clinically meaningful average group difference on the integrated Alzheimer's Disease Rating Scale compared to placebo.[1] Lecanemab therapy achieved less than half of the estimated MCID on the CDR-SB, while the attenuation of change on the ADAS-Cog at 18 months was half of that achieved by donepezil at 6 months, notwithstanding the risk of ARIAs and the consistent association with progressive cerebral atrophy.[17] Cost-effectiveness estimates do not favor lecanemab therapy over the standard of care even if *APOE* ε4 carrier status is considered.[18] Identifying subgroups of better responders, particularly with treatment earlier in the course of the disease, a longer follow-up,[7] and the perspective of combination therapies[14] could help improve their clinical relevance, though clinically meaningful harms including death may still prevent wider acceptance.[19]

Although therapy with cholinesterase inhibitors and memantine is associated with statistically significant improvements in cognitive function in patients with dementia, the clinical meaningfulness derived from such treatment is not entirely clear. One network meta-analysis[20] found that they are overall safe but had variable (though modest) effects on cognition and behavior according to MCIDs and global ratings, either in isolation or when a combination of donepezil with memantine was used. Still, cholinesterase inhibitors and memantine remain the best options for therapy of AD given their outcomes on MCIDs and their safety profiles.

Most clinical trials list a few demographic and anthropometric variables (such as sex, age, and body mass index) but seldom take them into account in the analyses,[1] rather restricting their exclusion criteria to participants with unstable cardiovascular diseases. This strategy can be misleading for several reasons, such as older patients with arterial hypertension who have "normal" blood pressure under pharmacological therapy declining faster due to relative brain hypoperfusion.[6] Many

trials only include one or two genetic variants of interest, while others do not include any.[11] The impact of all genes of interest on the outcomes of clinical trials is hard to quantify, but is certain to affect the significance of the findings.

The universal use of MCIDs should be implemented when outcomes are not susceptible to translation into absolute benefits. Statistical analyses adopting MCIDs ("responder analyses") are not formally required by regulatory authorities for clinical trial approval. Statistical adjustment of the significance of MCIDs according to multiple comparisons is essential for the external validity of research results. Application of trial results to individual patients must require that MCIDs be met at the population level. Wider inclusion of confounding factors in the statistics may help bring trial results closer to real-world conditions, though such factors must be carefully selected not to compromise the statistical significance of the analyses.

AUTHOR CONTRIBUTIONS

Fabricio Ferreira de Oliveira remains fully responsible for the conceptualization, writing of the original draft, review, and editing of this article.

ACKNOWLEDGMENTS

The author acknowledges the support of the Department of Neurology and Neurosurgery and the Department of Morphology and Genetics of the Federal University of São Paulo – UNIFESP that allowed the research that resulted in his current views to be published. The author also thanks the editors for the waiver that allowed him to write for the Minimal Clinically Important Differences Special Issue.

CONFLICTS OF INTEREST STATEMENT

Fabricio Ferreira de Oliveira, MD, BBA, MSc, PhD, FAAN, is a medical researcher of the Department of Neurology and Neurosurgery of the Federal University of São Paulo – UNIFESP, a Fellow of the American Academy of Neurology and a Member of the American Academy of Neurology Global Strategies Subcommittee (AAN, 2021-2027), of the Committee of Experts of the European Science Foundation, of the Awards Committee of the International Parkinson and Movement Disorder Society (MDS, 2021–2025), and of the Executive Committees of the ISTAART Biofluid Based Biomarkers Professional Interest Area (Alzheimer's Association, 2018–2025) and the ISTAART Neuropsychiatric Syndromes Professional Interest Area (Alzheimer's Association, 2024–2026). He has received research support from CAPES—*Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* and FAPESP – The State of São Paulo Research Foundation, and serves as a health-care council member for Gerson Lehrman Group, for Atheneum Partners, for Guidepoint, and Lionbridge. The author is also an Editorial Board Member of *Neurology*, *Medicine*, *Clinical Neurology & Neurosurgery*, *Frontiers in Neuroscience*, *Neurology Letters*, and the *Journal of Alzheimer's Disease*—JAD. Author disclosures are available in the supporting information.

ORCID

Fabricio Ferreira de Oliveira https://orcid.org/0000-0002-8311-0859

REFERENCES

1. Muir RT, Hill MD, Black SE, Smith EE. Minimal clinically important difference in Alzheimer's disease: rapid review. *Alzheimers Dement*. 2024;20:3352-3363.
2. 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*. 2019;5:354-363.
3. Stojanovic M, Mikula C, John S, Kiselica A. Clinical importance in Alzheimer's disease: effects of anchor agreement and disease severity. *Aging Clin Exp Res*. 2024;36:5.
4. Cummings J. Meaningful benefit and minimal clinically important difference (MCID) in Alzheimer's disease: open peer commentary. *Alzheimers Dement*. 2023;9:e12411.
5. Berthier ML, Hinojosa J, Martín Mdel C, Fernández I. Open-label study of donepezil in chronic poststroke aphasia. *Neurology*. 2003;60:1218-1219.
6. de Oliveira FF, de Almeida SS, Chen ES, Smith MC, Naffah-Mazzacoratti MG, Bertolucci PHF. Lifetime risk factors for functional and cognitive outcomes in patients with Alzheimer's disease. *J Alzheimers Dis*. 2018;65:1283-1299.
7. Tarawneh R, Pankratz VR. The search for clarity regarding "clinically meaningful outcomes" in Alzheimer disease clinical trials: *CLARITY-AD and Beyond*. *Alzheimers Res Ther*. 2024;16:37.
8. de Oliveira FF, de Almeida SS, Chen ES, Smith MC, Bertolucci PHF. APOE ε4 carrier status as mediator of effects of psychotropic drugs on clinical changes in patients with Alzheimer's disease. *J Neuropsychiatry Clin Neurosci*. 2022;34:351-360.
9. De Oliveira FF, Miraldo MC, de Castro-Neto EF, et al. Differential associations of clinical features with cerebrospinal fluid biomarkers in dementia with Lewy bodies and Alzheimer's disease. *Aging Clin Exp Res*. 2023;35:1741-1752.
10. Silva NCBS, Bracko O, Nelson A, et al. Vascular cognitive impairment and dementia: An early career researcher perspective. *Alzheimers Dement*. 2022;14:e12310.
11. Oliveira FF. Looking behind the curtain: patient stratification according to genetic or demographic factors may yield unexpected results in studies of neurodegenerative diseases. *J Alzheimers Dis*. 2023;94:777-780.
12. Boccardi M, Monsch A, Ferrari C, et al. Harmonizing neuropsychological assessment for mild neurocognitive disorders in Europe. *Alzheimers Dement*. 2022;18:29-42.
13. Pittock RR, Aakre JA, Castillo AM, et al. Eligibility for Anti-amyloid treatment in a population-based study of cognitive aging. *Neurology*. 2023;101:e1837-e1849.
14. Cummings JL, Tong G, Ballard C. Treatment combinations for Alzheimer's disease: current and future pharmacotherapy options. *J Alzheimers Dis*. 2019;67:779-794.
15. de Oliveira FF, Bertolucci PH, Chen ES, Smith Mde A. Pharmacological modulation of cognitive and behavioral symptoms in patients with dementia due to Alzheimer's disease. *J Neurol Sci*. 2014;336:103-108.
16. Lacorte E, Ancidonia A, Zaccaria V, et al. Safety and efficacy of monoclonal antibodies for Alzheimer's disease: a systematic review and meta-analysis of published and unpublished clinical trials. *J Alzheimers Dis*. 2022;87:101-129.
17. Nadeau SE. Lecanemab questions. *Neurology*. 2024;102:e209320.
18. Nguyen HV, Mital S, Knopman DS, Alexander GC. Cost-effectiveness of lecanemab for individuals with early-stage Alzheimer disease. *Neurology*. 2024;102:e209218.

19. Ebell MH, Barry HC, Baduni K, Grasso G. Clinically important benefits and harms of monoclonal antibodies targeting amyloid for the treatment of Alzheimer disease: a systematic review and meta-analysis. *Ann Fam Med*. 2024;22:50-62.
20. Tricco AC, Ashoor HM, Soobiah C, et al. Comparative effectiveness and safety of cognitive enhancers for treating Alzheimer's disease: systematic review and network metaanalysis. *J Am Geriatr Soc*. 2018;66:170-178.

SUPPORTING INFORMATION

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

How to cite this article: de Oliveira FF. The problem of multiple adjustments in the assessment of minimal clinically important differences. *Alzheimer's Dement*. 2025;11:e70032. https://doi.org/10.1002/trc2.70032