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REPLY

Response to van Dyck, O'Dell, & Mecca letter to the editor regarding Andrews et al. (2019)

In their letter to the editor, van Dyck et al. commented on our 2019 paper "Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials,"[1] as well as its interpretation, application, and use in subsequent research. While we wholeheartedly agree with van Dyck et al. regarding the importance of appropriate interpretation of our findings in the context of clinical trial results with need for more refined definitions of clinical meaningfulness, we disagree with their narrow characterization of our approach, as discussed further below.

van Dyck et al. assert that "[Question 3a in the relevant NACC UDS form (uds2-fvp-b9)] is intended to differentiate an acquired cognitive disorder from lifelong impairment e.g., 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." However, they provide no evidence that responding clinicians indeed interpreted Question 3a in that manner. In fact, the wording of the NACC UDS Coding Guidebook creates considerable uncertainty as to how the question should be interpreted. For example, the question asks whether there is a "current meaningful decline" in the subject's abilities and requires physicians to provide a response at every visit.[2] Similarly, regarding cognitive function, the guidebook states that: "Cognitive decline refers to changes in the subject's usual or customary memory or non-memory cognitive abilities reported or observed at the current visit."

To support their interpretation of Question 3a, van Dyck et al. point to the findings reported in Figure S1 of our 2019 paper regarding the proportion of visits coded with clinically meaningful decline by disease severity. However, considering the progressive nature of the disease, it is not unexpected that people with higher disease severity continue to experience an incremental, meaningful decline in cognitive and functional abilities over time. Indeed, these findings are consistent with reported trajectories of decline in clinical measures observed among individuals with Alzheimer's disease (AD) more broadly.[3–5]

Given the uncertainty in how clinicians may have interpreted Question 3a underlying our anchor-based measures, it is important to further examine the external validity of our findings. Indeed, our findings are consistent with other anchor-based findings reported in the literature, including a secondary anchor measure reported in our 2019 paper. Specifically, we conducted a sensitivity analysis using a change in global CDR from 0.5 to 1 as an anchor and found similar results as in the core analyses (see Table 5 of our 2019 paper).[1] More recently, using a different dataset and different anchor measures, Lansdall et al. also reported comparable estimates for within-patient minimal clinically important difference (MCID) over 12-month intervals.[6]

van Dyck et al. further commented that "determination of meaningful decline is driven by the duration of the follow-up period in the NACC UDS (one year). […] By this standard then, a therapeutic agent would essentially need to halt progression to have a clinically meaningful effect." We agree that our estimates may overstate MCID due to the typical 1-year interval between assessments in the NACC data, and discussed this in our original paper, along with other potential limitations. Indeed, Lansdall et al. more recently estimated MCIDs at different intervals and reported somewhat smaller estimates at 6 months compared to 12 months.[5] Most importantly, however, we observe that the findings from our paper and similar research efforts have often been misinterpreted or misapplied.[7,8] As further clarified recently in Petersen et al.,[9] these estimates should be used to infer meaningful within-patient disease progression, and not clinical meaningfulness of differences between groups of patients.

In conclusion, despite concerns raised by van Dyck et al. regarding the primary anchor used in our study, our findings are consistent with identifiable patterns of clinical disease progression across the continuum of AD; a companion sensitivity analysis reported in our paper; and more recently, published estimates of within-patient clinically meaningful changes using a different dataset and anchor. We fully agree that there is a need to refine the definitions of clinical meaningfulness of disease progression in AD, with the aim to inform interpretation of between-group differences evaluated in clinical trials, and in doing so, we encourage the field to move toward incorporating patient and caregiver perspectives.

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The authors have nothing to report.

CONFLICT OF INTEREST STATEMENT

Jeffrey Scott Andrews was an employee of Eli Lilly and Company at the time of the original study and is currently an employee of Takeda Pharmaceutical Company Limited. Urvi Desai and Noam Kirson are

employees of Analysis Group, Inc., a consulting firm that received funding from Eli Lilly and Company for the original research. Brandy Matthews is an employee of Eli Lilly and Company. Author disclosures are available in the supporting information.

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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. doi:10.1016/j.trci.2019.06.005. PMID: 31417957; PMCID: PMC6690415.
2. *See*, NACC Uniform Data Set (UDS) Coding Guidebook for Initial Visit Packet (v. 2.0), page 34, Available at: https://files.alz.washington.edu/documentation/uds2-ivp-guidebook.pdf; and NACC Uniform Data Set (UDS) Coding Guidebook for Follow-up Visit Packet (v. 2.0), page 29, Available at: https://files.alz.washington.edu/documentation/uds2-fvp-guidebook.pdf
3. Samtani MN, Raghavan N, Novak G, Nandy P, Narayan VA. Disease progression model for clinical dementia rating-sum of boxes in mild cognitive impairment and Alzheimer's subjects from the Alzheimer's Disease Neuroimaging Initiative. *Neuropsychiatr Dis Treat* 2014;10: 929-952.
4. Davis M, O Connell T, Johnson S, et al. Estimating Alzheimer's disease progression rates from normal cognition through mild cognitive impairment and stages of dementia. *Curr Alzheimer Res*. 2018;15(8):777-788.
5. Parnetti L, Chipi E, Salvadori N, D'Andrea K, Eusebi P. Prevalence and risk of progression of preclinical Alzheimer's disease stages: a systematic review and meta-analysis. *Alzheimers Res Ther*. 2019;11(1):7. doi:10.1186/s13195-018-0459-7
6. Lansdall CJ, McDougall F, Butler LM, et al. Establishing clinically meaningful change on outcome assessments frequently used in trials of mild cognitive impairment due to Alzheimer's disease. *J Prev Alzheimers Dis*. 2023;10:9-18. doi:10.14283/jpad.2022.102
7. Institute for Clinical and Economic Review (ICER) Alzheimer's Disease – Evidence. Report March 2023, Page 10.
8. Lacorte E, Ancidoni 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(1):101-129.
9. Petersen RC, Aisen PS, Andrews JS, et al. Expectations and clinical meaningfulness of randomized controlled trials. *Alzheimer's Dement*. 2023;1-7. doi:10.1002/alz.12959

SUPPORTING INFORMATION

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