

Poor Performance on Diagnostic Tests in Early Dementia Clinical Trials as a Marker of Possible Score Inflation. An Exploratory Analysis

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SUBMISSION DETAILS

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Methodological Issue Being Addressed A novel approach to recognize and address potential score inflation for Dementia clinical trial inclusion.

Introduction The success of any clinical trial begins with ensuring that participants entering the trial meet the inclusion and disease severity criteria. Score manipulation to meet eligibility criteria may contribute to loss of signal in clinical trials. Based on our prior analyses of early Alzheimer's disease (AD) clinical trials, over 10% of randomized participants likely had MMSE scores at inclusion determination that were either intentionally or unintentionally inflated (higher). This means that these patients were, in reality, more cognitively impaired than required by the protocol and than their inclusionary MMSE scores would indicate. In addition to 'traditional' instruments such as the MMSE or CDR, other cognitive performance instruments such as the RBANS, FCSRT and Wechsler Memory Scale are often used to select the study population. In the current analysis, we explore the relationship between the performance on the cognitive performance tests and the likely inflation in the MMSE (artificially higher MMSE scores), and assess whether poor performance on these tests could be used as a risk indicator of possible score inflation.

Methods Baseline MMSE scores and Screening cognitive performance instrument results were pooled from 7,648 subjects from multiple clinical trials in early AD. Within each trial, participants' performance on the cognitive performance instruments was broken into quartiles – best performers, second best, second worst and worst performers. Participants were also classified by their Baseline MMSE score as either meeting or being below the Screening MMSE inclusion criteria. A logistic regression was used to explore the association of the cognitive performance instrument performance quartiles and Baseline MMSE score categories, correcting for Screening MMSE score. Sensitivity and specificity was calculated for the worst performers quartile used as a risk indicator of possible score inflation.

Results 1,547 (20.2%) participants comprised the best performing quartile on the cognitive performance instruments. Comparatively, with each subsequent quartile, the odds of not meeting the Screening inclusion criteria at Baseline increased significantly - by 1.5x in the 1,954 participants (25.5%) in the second best, by 1.8x in the 1,464 (19.3%) in the second worst, and by 2.6x in the 2,687 (35.1%) in the worst quartile. The sensitivity of the risk indicator based on worst performance on the cognitive performance instruments was 53.4% and the specificity 68.4%.

Conclusion This post-hoc analysis identified increasingly significant odds of not meeting Screening MMSE related inclusion criteria at Baseline for each progressive quartile of worsening cognitive

performance instrument performance, when correcting for the Screening MMSE score. Additionally, over 50% of subjects with likely inflated MMSE scores at Screening were categorized as worst performers on the cognitive performance instruments. We therefore suggest that despite the limitations of this post-hoc analysis, outlying poor performance on the cognitive performance instruments should be considered a risk marker for possible MMSE score inflation. However, to prevent false positives, other risk markers (e.g. - MMSE interview duration) need to be considered in the context of the available data.

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Guidelines I have read and understand the Poster Guidelines

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