# Impact of Independent Review on Potential MMSE Score Inflation at Screening in AD trials

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### BACKGROUND

The Mini-Mental State Examination (MMSE) [1] is widely used as a screening tool in Alzheimer's Disease (AD) clinical trials (2). Screening score inflation, truncated scores at the inclusion criteria cut-off, is documented in clinical trials of depression and anxiety (3, 4). To mitigate inclusionary bias and minimize administration and scoring errors, different methodologies, including Independent Ratings (IR) and Independent Review (IRev), have been implemented (3, 4). IRev is employed in AD trials where site-based assessments are audio recorded and routed to an independent reviewer to verify the quality of administration and score accuracy of select assessments.

# **OBJECTIVES**

We investigated whether score distributions on several multi-site multinational AD trials showed truncated scores around MMSE inclusion criteria cut-off, and whether IRev is an effective methodology to mitigate inclusion bias.

## METHODS

MMSE screening score distributions from several multinational clinical trials of Early Symptomatic and Mild to Moderate AD were examined. Site raters underwent a rigorous pre-screening, qualification, and certification process prior to rating the MMSE. To assess the impact of IRev on screening score distribution, we compared two studies with similar inclusion criteria (Early AD, MMSE ≥ 22; CDR GS = 0.5 or 1) one with no IRev and one with IRev via audio recording. IRev was performed on the first two MMSE assessments completed by each MMSE rater, plus additional reviews if any of the two reviewed assessments were deemed as not meeting quality or scoring criteria.

# REFERENCES

1. Folstein MF, Folstein SE, McHugh PR: "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975, 12(3):189-198



## RESULTS

MMSE screening frequency distributions showed an unusual increase at inclusion threshold for the No-IRev group compared to IRev. Kolmogorov Smirnov (KS) tests were performed to determine whether the distributions with and without IRev were drawn from the same population. There was a statistically significant difference in score distributions between IRev and No-IREV groups (p < 0.001), (Figure 1). The frequency distributions for the two groups were also compared using several score ranges around the threshold (21-23, 20-24, 19-25, and 18-26) with Chi-squared tests. Significant group differences were observed across the score ranges; 21-23 (X2 = 17.96, df =2, p < 0.01), 20-24 (X2 = 23.56, df = 4, p < 0.01), 19–25 (X2 = 32.65, df = 6, p < 0.01), and 18–26 (X2 = 54.96, df = 8, p < 0.01), suggesting a smaller inclusion bias around the threshold in the IRev group (Figure 2).

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# CONCLUSION

Sites are faced with pressure to enroll study participants and provide potential treatment to patients under their care. This pressure may lead to leniency in scoring some items in the MMSE to ensure subjects who are very close to the entry criteria are enrolled. In this project, we found that screening score inflation, which has been documented in depression and anxiety clinical trials, also occurs in AD trials. Additionally, implementing Independent Review as a monitoring strategy appears to be effective at reducing the number of subjects who are inappropriately enrolled in the study. Moreover, IRev may be most effective when applied to assessments that fall around the required scored for study participation, as opposed to rater-based algorithms (e.g. first assessment or two per rater).

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