MMSE and CDR Score Changes and Potential Score Inflation in Multinational Alzheimer's Disease Trials

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BACKGROUND

- In Alzheimer's Disease trials, the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR) are commonly utilized as inclusionary criteria at screening.
- These measures, however, do not always reaffirm inclusionary status at baseline.
- Score changes between screening and baseline visits may imply potential score inflation at screening leading to inappropriate participant enrollment.
- This study compared score changes in global AD trials when MMSE and CDR scores were used as inclusionary measures at screening only versus screening and baseline visits.
- We hypothesized greater score changes would be observed in trials utilizing these inclusionary measures at screening alone.

METHOD

- This study incorporated electronic scale (eScale) data from three global Phase 3 trials comprised of MCI to Mild AD participants, where the MMSE and CDR were used as inclusionary criteria.
- Two studies applied inclusion scoring criteria at screening, while one study applied inclusion scoring criteria at both screening and baseline.
- All raters completed Signant Health standardized rater training and certification programs.
- eScales and data quality monitoring programs increased rater scoring accuracy.
- Mann-Whitney U tests and t-tests were conducted comparing score changes on MMSE total score and CDR Domain and Global Scores.

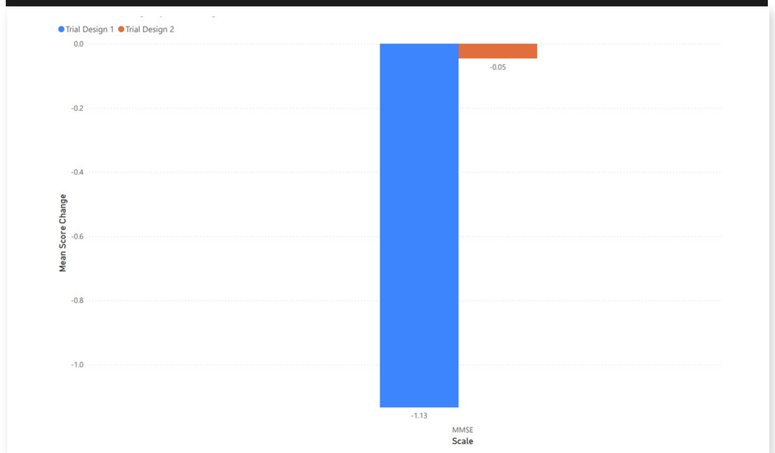
RESULT

- Both Mann-Whitney U and t-tests revealed significant differences in score changes between screening and baseline visits for the two trial designs, including all domain and total scale scores, except for the CDR Personal Care domain ($p<0.001$), as seen in Table 1.
- Increased scores for the CDR domain/Global scores and reduced scores on MMSE were observed when inclusionary criteria were required at screening alone.

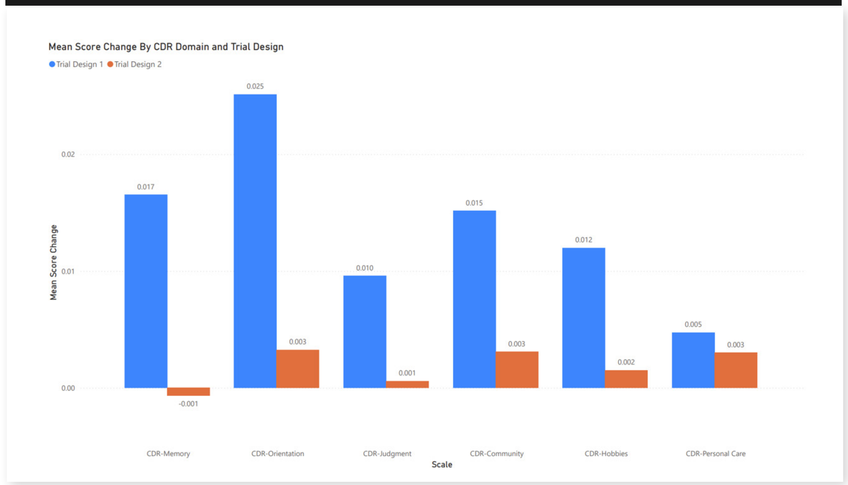
TABLE 1. MEAN DIFFERENCES IN SCORE CHANGES FOR MMSE AND CDR SCORES BETWEEN TRIAL DESIGNS

Scale	Mean Score Change for *Trial Design 1*—MMSE and CDR inclusionary at Screening only (n)	Mean Score Change for *Trial Design 2*—MMSE and CDR Inclusionary at Screening and Baseline (n)	Mean Difference in Score Change
MMSE	-1.133 (5602)	-0.046 (3046)	1.087*
CDR-GS	0.027 (5532)	0.008 (2986)	0.019*
CDR-Memory	0.017 (5624)	-0.001 (2986)	0.018*
CDR-Orientation	0.025 (5624)	0.003 (2986)	0.022*
CDR-Judgment	0.010 (5624)	0.001 (2986)	0.009*
CDR-Community	0.015 (5624)	0.003 (2986)	0.012*
CDR-Home and Hobbies	0.012 (5624)	0.002 (2986)	0.010*
CDR-Personal Care	0.005 (5624)	0.003 (2986)	0.002

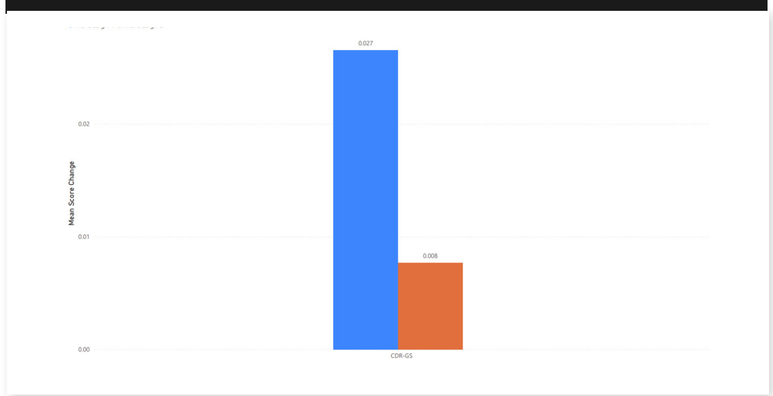
MMSE- MEAN SCORE CHANGE BY TRIAL



CDR DOMAINS - MEAN SCORE CHANGE BY TRIAL DESIGN



CDR GLOBAL SCORE - MEAN SCORE CHANGE BY TRIAL DESIGN



CONCLUSION

- The present study found greater score changes in the CDR and MMSE for participants who met inclusion criteria at screening only compared to both screening and baseline.
- These findings suggest potential score inflation at inclusionary visits when inclusionary scoring is required only at screening.
- To reduce inclusionary bias and inappropriate participant enrollment, a data quality surveillance program is recommended at inclusionary and subsequent visits throughout the study.
- Future studies should explore additional factors contributing to score change.

Disclosures: All authors are full-time employees of Signant Health.
Presentation and associated analyses financially supported by Signant Health

Presented at Alzheimer's Association International Conference | July 28 - Aug 1, 2024 | Philadelphia, PA

SIGNANT HEALTH

Impact of Site Size on Data Quality in Early Alzheimer's Disease Clinical Trials

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BACKGROUND

- Clinical trial sponsors rely on research sites to identify and enroll appropriate study participants and to correctly and reliably assess symptom severity and function over the course of the trial.
- Low-recruiting sites represent a large financial and operational burden and may negatively impact trial success either by selecting inappropriate participants and/or having a high prevalence of data quality issues.
- We previously reported that >60% of sites in schizophrenia clinical trials recruited ≤5 participants.
- Here we analyze 3 large dementia trials to assess the proportion of low-recruiting sites and compare their data quality with the remaining sites

METHOD

- Data were obtained from 3 global early dementia clinical trials conducted in 41 countries world-wide totaling 834 sites.
- Sites were divided into two groups based on the number of randomized subjects:
  1. High-recruiting sites: sites with more than 5 randomized subjects
  2. Low-recruiting sites: sites with 5 or less randomized subjects
- Data quality issues were defined as administration and scoring errors on relevant scales.
- These errors were summed per site and then compared by site size using Poisson regression with the site size, study and their interaction as predictors and the number of possible hits as exposure.

RESULTS

- 71 (8.5%) sites did not randomize a subject, 43 (5.2%) sites randomized one subject, and 377 (45.2%) sites randomized ≤5 subjects. (Figure 1)
- Overall, administration and scoring errors were more frequent at low-recruiting sites (seen at 41.9% visits) compared to 35.3% at the high-recruiting sites.
- 2 studies show significantly higher Incidence Rate Ratios (IRR), 1.59 (1.46,1.74) and 1.2 (1.15, 1.25) respectively, indicating more data quality issues at low-recruiting sites, while the third study has an IRR close to 1 but not statistically significant. (Figure 2)

CHARTS AND FIGURES

FIGURE 1: BREAKDOWN OF SITES BY NUMBER OF SUBJECTS RANDOMIZED

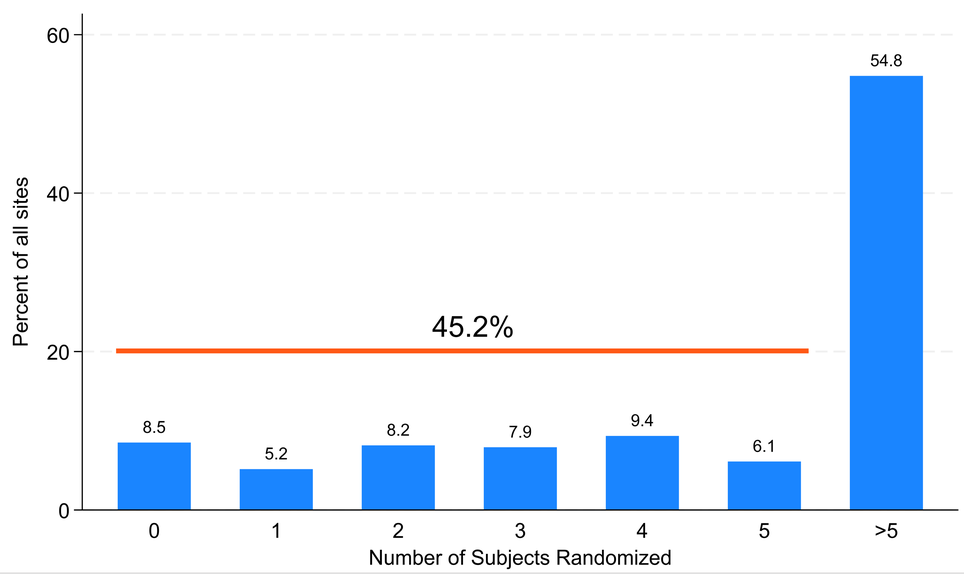
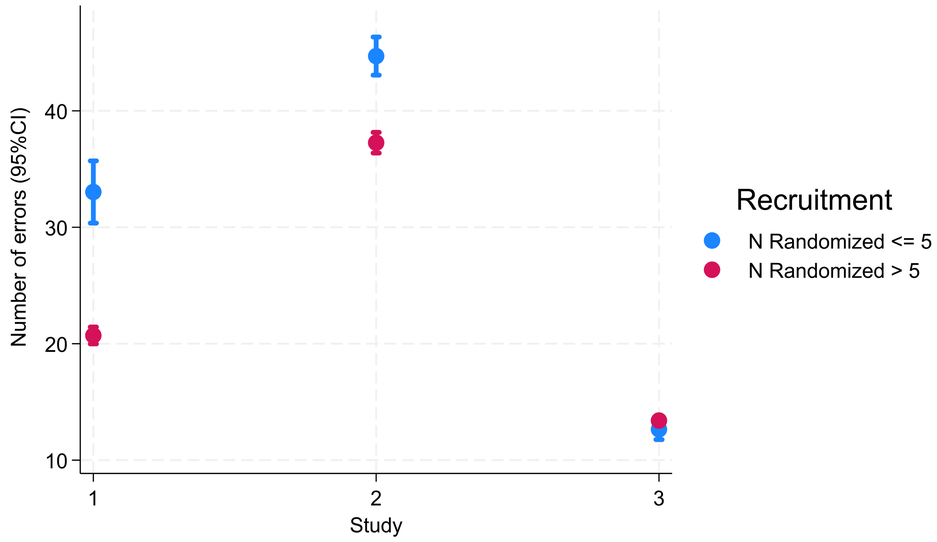


FIGURE 2: NUMBER OF ERRORS BY RECRUITMENT



CONCLUSION

- Our results indicate that low-recruiting sites (arbitrarily defined as randomizing ≤5 participants) are frequent in large dementia trials.
- These sites pose considerable cost to sponsors, but more importantly, are more likely to provide questionable data quality.
- While a single site like this only represents a small risk, in aggregate, they can pose a serious challenge.
- Clinical trial sponsors should therefore consider strategies to minimize the impact of low-recruiting sites on study outcomes.

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Presentation and associated analyses financially supported by Signant Health

Presented at Alzheimer's Association International Conference | July 28 - Aug 1, 2024 | Philadelphia, PA

SIGNANT HEALTH

Impact of Rater Change on MMSE Data: A Post-Hoc Analysis

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INTRODUCTION

- Rater change is inevitable in often lengthy clinical trials in Alzheimer's disease.
- Other groups have previously assessed the impact of rater change on data variability.
- Their conclusions varied, possibly due to differing methodologies (e.g. - comparing actual vs. absolute change; analyzing data per trial and visit or by combining all trials and visits).
- Here, we analyze the impact of rater change of MMSE data - using both actual and absolute change - looking only between Screening and Baseline visits.

METHOD

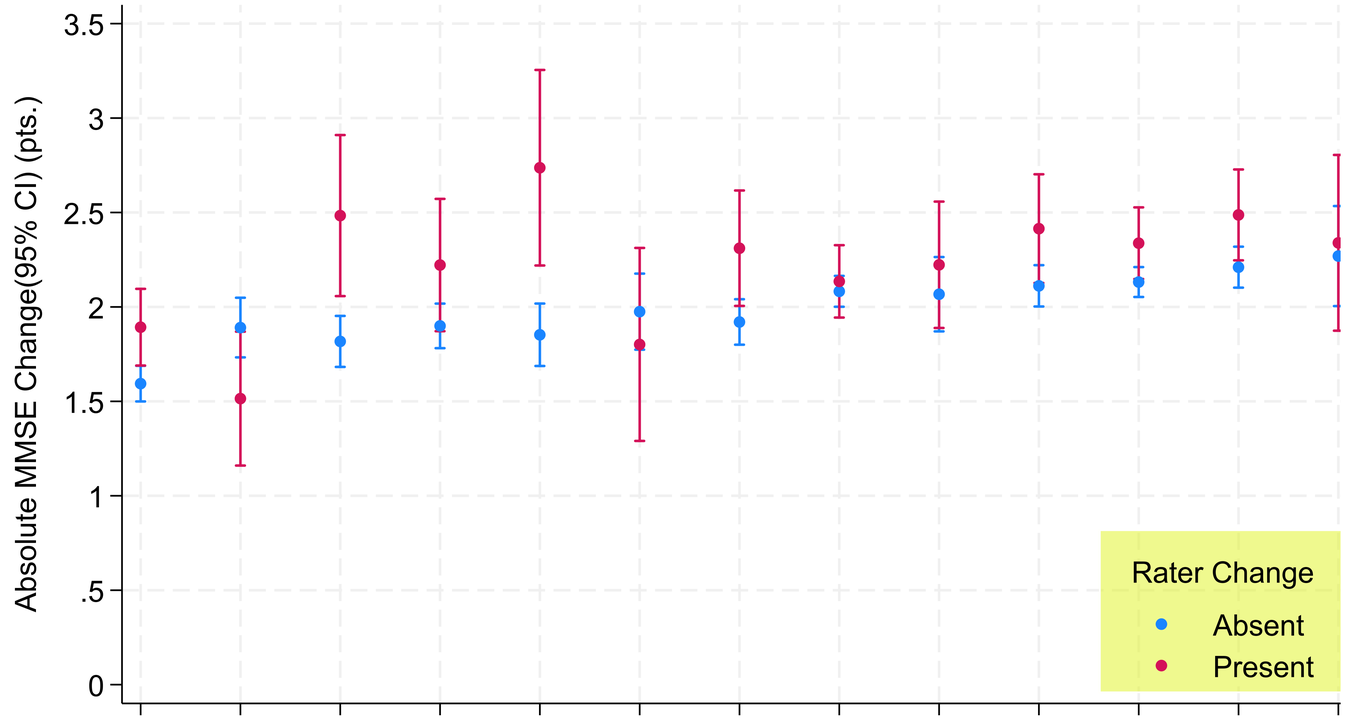
- MMSE scores and MMSE score change from 11,084 Screening to Baseline assessments were collected from 13 Alzheimer's disease clinical trials.
- Data were broken into 2 groups - those with and without rater change between Screening and Baseline visits.
- Two regression models were fitted to the data.
  - In the first model, the dependent variable was the MMSE actual change (improvement or worsening) from Screening to Baseline.
  - In the second model, the dependent variable was the MMSE absolute change (magnitude of change) from Screening to Baseline.
  - Rater change, clinical trial and their interaction were used as predictors and MMSE Baseline value entered in a cubic form as a covariate.

RESULTS

- In the first model using actual MMSE change, neither rater change, nor the interaction between protocol and rater change was significant.
- Removing the interaction term, rater change decreased the MMSE change by 0.1 MMSE points (p = 0.06).
- In the second model, the effect of rater change differed from study to study. Among studies that showed significant rater change effect, the absolute MMSE change increased by 0.46 points on average. (Figure 1)

CHARTS AND FIGURES

FIGURE 1. IMPACT OF RATER CHANGE ON MMSE SCREENING-TO BASELINE ABSOLUTE CHANGE



DISCUSSION

- Our results indicate that rater change may indeed have an impact on MMSE data, but the impact is inconsistent.
- While the actual change was affected only insignificantly, the absolute change as a measure of variability was significantly increased.
- Substantial differences were observed between individual studies and in only 6 of the 13 studies, rater change significantly increased MMSE absolute change.
- Given the results, rater change should be considered a risk factor to assessment reliability and reasonable efforts should be taken to minimize both its occurrence and its impact on study data.

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Presentation and associated analyses financially supported by Signant Health

Presented at Alzheimer's Association International Conference | July 28 - Aug 1, 2024 | Philadelphia, PA

SIGNANT HEALTH

Geo-cultural Variation in MMSE Score Changes from Screening to Baseline in Alzheimer's Disease Trials

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BACKGROUND

- The Mini-Mental State Examination (MMSE) is one of the most extensively utilized screening tools in Alzheimer's disease (AD) clinical trials.
- Previous studies (e.g., Echevarria, 2023) have identified instances of MMSE screening score inflation when the scale is employed as an inclusion criterion, potentially leading to the inappropriate enrollment of participants and complicating the detection of treatment effects.
- Recent research by Hackebeil et al. (2024) compared score changes in multinational AD trials where MMSE was used solely at screening versus at both screening and baseline visits. They observed greater score changes in the former, suggesting possible screening score inflation in multinational AD trials.
- However, the universality of this phenomenon across geo-cultural regions in AD trials and potential variations remain underexplored.
- This study aims to investigate whether MMSE score changes from screening to baseline vary across geo-cultural regions in multinational AD trials, including North America, Asia, Eastern Europe, Western Europe, Latin America, and the Middle East/Africa

METHOD

- Data were analyzed from two multinational Phase 3 AD trials, wherein MMSE served as an inclusion criterion at screening but not at baseline. Both studies adhered to the same MMSE cut-off for inclusion.
- All raters received standardized training and certification for MMSE administration. An enhanced eMMSE scale was employed to reduce rater errors, complemented by a data quality surveillance program that included central audio review of eMMSE administration and scoring.
- Statistical analyses were conducted using Kruskal-Wallis and Dunn's tests to compare score changes from screening to baseline across different regions.

RESULT

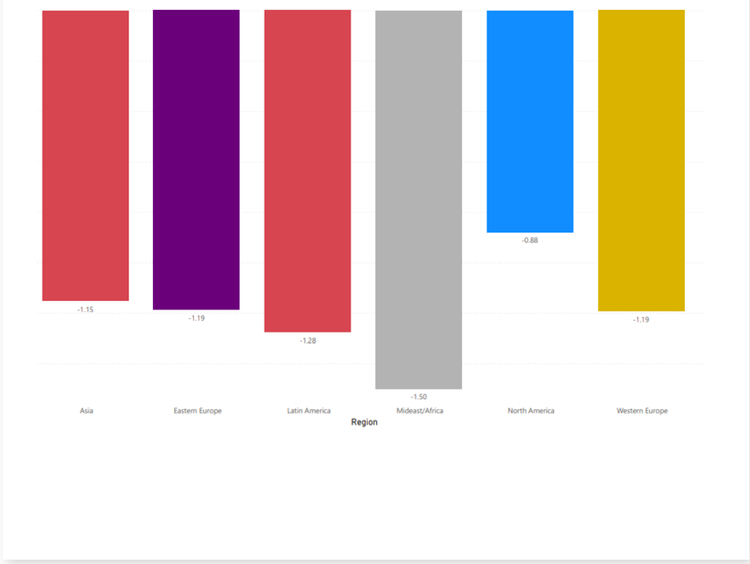
- Both Mann-Whitney U and t-tests revealed significant differences in score changes between screening and baseline visits for the two trial designs, including all domain and total scale scores, except for the CDR Personal Care domain ($p<0.001$), as seen in Table 1.
- Increased scores for the CDR domain/Global scores and reduced scores on MMSE were observed when inclusionary criteria were required at screening alone.

TABLE 1. MEAN MMSE TOTAL SCORE CHANGE ACROSS REGIONS

Geo-Cultural Regions (n)	Mean MMSE Score at Screening	Mean MMSE Score at Baseline	Mean MMSE Total Score Change (SD)
Asia (n = 1000)	24.12 (3.792)	23.77 (3.126)	-1.149 (2.609)
Eastern Europe (n = 811)	24.91 (3.148)	23.89 (3.129)	-1.188(2.632)
Latin America (n = 427)	24.06 (3.888)	23.82 (3.277)	-1.277 (2.742)
Middle East/Africa (n = 163)	24.36 (3.800)	23.490 (3.162)	-1.500 (2.587)
North America (n = 1317)	24.34 (3.978)	24.03 (3.192)	-0.884 (2.568)*
Western Europe (n = 2074)	24.21 (3.646)	23.90 (3.079)	-1.188 (2.519)

**Different from the rest of regions on Dunn's tests (p<.001)*

CHART 1. MEAN TOTAL SCORE CHANGE BY REGION



CONCLUSION

- The study identified geo-cultural variations in potential MMSE "screening inflation" within multinational AD trials.
- North America exhibited a significantly smaller score decrement than other regions, suggesting lesser MMSE score inflation at inclusionary visits in this region.
- The geo-cultural differences in MMSE screening inflation may be partly attributed to cultural factors that influence placebo responses. Previous research has highlighted the impact of cultural effects on placebo and nocebo phenomena, affecting therapeutic expectations, disease perceptions, and treatment interactions (Cundiff-O'Sullivan et al., 2023).
- Further investigation is warranted to elucidate the factors driving these geo-cultural disparities in MMSE screening inflation and their implications for AD trials.

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Presented at Alzheimer's Association International Conference | July 28 - Aug 1, 2024 | Philadelphia, PA

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