Increased Signal Detection in Alzheimer’s Disease Clinical Trials – Improving the Probability of Technical and Regulatory Success

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BACKGROUND

- It is commonly believed that longer lag times between administrations of clinical outcome assessments (COAs) are likely to contribute to increased errors.
- Typical remedies include rater training such as didactic tutorials, qualification post-tests and scoring of video-based rating precision exercises1-2. These are typically completed before site/study initiation, however, and therefore unlikely to prevent rater drift over time.
- Another potential solution includes administration of measures using a tablet device and electronic clinical outcome assessments (eCOA), which has been demonstrated to result in fewer errors than paper and pen administration.
- However, there is limited empirical data on the impact of administration lag time on error rates and whether eCOA administration also attenuates the effect of lag time on error rates.
- This study investigated the impact of lag time on error rates for commonly used Alzheimer’s disease (AD) COAs, as well as the degree to which administration (eCOA versus paper and pen) attenuated error rates associated with lag time.
- Objectives:
  - Determine the impact of lag time on error rates of COAs commonly used in AD clinical trials.
  - Examine whether use of eCOA versus paper and pen administration attenuates error rates attributable to lag time.

METHOD

- Data from three large early AD clinical trials (two MCI/MS/AD; one prodromal AD) were aggregated for commonly used AD COAs, namely, ADAS-Cog (n = 9,233), CDR (n = 5,146), MMSE (n = 2,657), RBANS (n = 1,385), and ADCS-ADL-MCI (n = 1,438).
- All trials involved standard rater training, including a mixture of didactic tutorials, qualification post-tests and rating precision exercises.
- Some of the assessments were administered using paper and pen: [ADAS-Cog: n = 8,162, CDR: = 2,859, MMSE: n = 957, RBANS: n = 855, and ADCS-ADL-MCI: n = 1,210].
- Other assessments were administered using a tablet device and eCOA: [ADAS-Cog: n = 1,071, CDR: = 2,287, MMSE: n = 1,700, RBANS: n = 530, and ADCS-ADL-MCI: n = 228].
- All assessments were audio recorded for quality assurance.
- A cohort of expert calibrated clinicians reviewed audio recordings and worksheets of the assessments and identified scoring discrepancies, regardless of administration format (paper and pen or eCOA).
- Assessment dates were used to calculate lag time in days between administrations of a given scale by site raters.

RESULTS

- The mean (standard deviation) administration lag times by scale are shown in Table 1. Average lag times varied by scale, with ADAS-Cog and CDR having shorter lag time compared to RBANS and ADCS-ADL-MCI.
- Figure 1 shows the frequency distributions for the lag times for each scale. For all the scales, the distribution was positively skewed to the right, with most of the data clustering towards the lower end of the distribution (short lag times).
- Overall scoring errors as a function COA administration lag time were also examined (Table 2). In linear regression models where administration lag time was entered as independent variable and scoring errors as dependent variable, lag time significantly predicted the probability of making an error on the subsequent administration for ADAS-Cog [estimate = 0.34; p < 0.001], CDR [estimate = 0.48; p < 0.001], and RBANS [estimate = 0.59; p < 0.027].
- Scoring accuracies were not significantly correlated with lag time for MMSE [estimate = 0.031; p = 0.11] or ADCS-ADL-MCI [estimate = 0.009; p = 0.739].
- As Table 2 indicates, there was a significant probability of making an error on subsequent administrations of ADAS-Cog (p < .0001) and CDR (p < .0001) on paper and pen that was mitigated when administered via eCOA (p-values > .05). The RBANS was borderline significant (p=.054) for paper and pen, also mitigated via eCOA (p>.739).
- Additionally, confirming our previously reported findings3, paper and pen administrations showed significantly higher scoring errors compared to eCOA on all the scales [ADAS-Cog: F(1, 9231) = 908.4 p<.0001; CDR: F(1, 5144) = 107.9 p<.0001; MMSE: F(1, 2655) = 724.5 p<.0001; RBANS: F(1, 1383) = 145.6 p<.0001; ADCS-ADL-MCI: F(1, 1436) = 8.9 p = .003].

DISCUSSION

- This study empirically demonstrated that increased lag time between administrations of COAs significantly increases error rates on ADAS-Cog, CDR and RBANS, three of the most commonly used and complex measures in AD clinical trials.
- As previously reported, overall error rates associated with lag time were substantially and significantly lower with eCOA administration via the Virgil tablet in comparison to paper and pen administration.
- ADCS-ADL-MCI and MMSE did not demonstrate an increased error rate as a function of lag time, but this may be attributable to fact that these scales are somewhat less demanding to score and require less knowledge of scoring rules.
- Overall error rates are substantially lower with eCOA administration compared to paper and pen administration, including error rates specifically associated with lag time between scale administrations.
- Rater training including didactic tutorials, qualification post-tests and rating precision exercises are necessary, but not sufficient, to prevent error variance and rater drift in clinical trials. Leveraging Central Review and eCOA administration via the Virgil tablet significantly helped decrease errors and prevent rater drift above and beyond this initial training, which increased the probability for signal detection and ultimately technical and regulatory success for these investigational clinical trials.

References