THE EFFICACY OF CENTRAL REVIEW MODALITIES IN THE QUALITY CONTROL OF ADAS-COG FOR AD CLINICAL TRIALS

INTRODUCTION

• The failure rate of Alzheimer’s disease (AD) trials is astoundingly high. Recent review of ongoing clinical trials has identified an overall success rate of 0.4 percent (99.6 percent failure) in AD trials – among the lowest for any therapeutic area (Cummings, et al., 2014).
• Variability in endpoint measurement is one likely contributor to the high failure rate. The Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-Cog), the most widely used endpoint in AD trials, is prone to high error rates that may contribute to unwanted variance (e.g., Shafer et al., 2011).
• Recognition of these high error rates has led to the use of centralized quality review methodologies to identify and correct such errors, thereby improving signal detection.

The goal of the present study was to compare the efficacy of two review modalities in the quality control of the ADAS-Cog: audio recordings vs. paper source documents.

METHODS

• Aggregated ADAS-Cog data from three double-blind, placebo-controlled AD clinical trials were reviewed.
• Assessments were centrally reviewed either via audio recordings or worksheet alone (Figure 1).
• Central Review was conducted by a highly trained and calibrated cohort of clinicians.
• Site raters underwent a rigorous pre-screening, training and qualification process prior to conducting in-study assessments.
• Raters were provided feedback regarding the administration of the scales, as well as scoring errors.

RESULTS

• Audio recordings review identified higher percentage of errors compared to paper source documents alone (Figure 2).
  – 56 percent of assessments reviewed via audio recordings were identified as having at least one error, in contrast to 17 percent identified through worksheet review alone.
  – Percentage of assessments identified as having two or more errors was also higher in audio recordings review (28 percent) compared to worksheet review alone (2 percent).

• The error rates declined over time for both review modalities (Figure 3).
  – Central Review of audio recordings identified higher percentage of errors throughout the observation period than paper worksheet review alone.

• Analysis of ADAS-Cog subtests identified score discrepancies in several components, particularly for the audio review (Figure 4).

CONCLUSIONS

• Central Review of audio recordings in ADAS-Cog is far more effective in identifying scoring errors than review of worksheets alone.
• The difference in results between the two modalities demonstrates that enabling the reviewer to hear the subject’s actual responses clearly improves the ability to detect additional errors not evident from the paper source alone.
• Review of audio recordings identified scoring discrepancies in almost all ADAS-Cog subtests, indicating the value of this approach in improving measurement reliability.
• Even with audio-based Central Review and feedback, however, error rates remain relatively high. This suggests that alternative approaches to administering neuropsychological tests such as the ADAS-Cog should be explored.

Neuropsychological test publishers have begun to utilize tablet PC platforms for test administration and scoring. This technology allows for the inclusion of additional clinical guidance in test administration, as well as automated scoring. The adaptation of this technology to clinical trials has the potential to further reduce error rates on scales such as the ADAS-Cog.

REFERENCES: