Assessing the impact of centralized data review on the reliability of the Alzheimer’s Disease Assessment Scale-Cognitive (ADAS-Cog)

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BACKGROUND

The Alzheimer’s Disease Assessment Scale Cognitive Subscale (ADAS-Cog) is the primary neurocognitive outcome measure in many clinical trials for mild-moderate Alzheimer’s disease (AD). Despite wide use, variations in administration and scoring are well-documented (1), and may reduce reliability and sensitivity of the measure (2). Variations in administration practices, misinterpretation of scoring rules, and intra-rater drift are among the greatest threats to psychometric reliability. Addressing these issues via rater education and centralized surveillance may increase reliability and sensitivity to treatment effects. Our goal was to quantify and compare variability in ADAS-Cog12 scores in the Critical Path Online Data Repository (CODR), and in the run-in phase of a recent multicenter, placebo-controlled treatment trial (NCT01852110) that incorporated centralized data surveillance, in order to assess the impact of centralized video/audio review on reliability across visits.

METHODS

Participants had mild-moderate AD with MMSE scores from 12-22 (inclusive). Data from two data sources were utilized:

Data Source 1: 13 studies in CODR, n=2,257, that included ADAS-Cog12, placebo arm data and were >6 months in duration.

- The CODR database is open to researchers and includes the results of clinical trials for AD submitted by a range of pharmaceutical companies. The database includes de-identified data of over 4,000 patients from eleven Alzheimer’s disease clinical trials. Additional information about this database and study sample is presented elsewhere (https://c-path.org/programs/camd/).

Data Source 2: Pre-treatment ADAS-Cog12 data (screening, run-in, baseline), n=355, from a multicenter, randomized, placebo-controlled trial (NCT01852110).

- In order to qualify for rater training and certification, potential raters were required to submit credentials for review and approval. Once approved, raters completed all training and certification activities prior to testing. Following each ADAS-Cog12 administration in the trial, source documents and video media were submitted for central review by expert data monitors.

RESULTS

For CODR, Absolute Agreement ICCs (0.810 (Visit 2), 0.760 (Visit 3)) showed a progressive decrease in correlations across time. The dataset that underwent data surveillance showed higher and increased Absolute Agreement ICCs (0.832 (Visit 2), 0.840 (Visit 3)). Cronbach’s α and test-retest intra class correlation coefficients for the ADAS-Cog scale were moderate to high between baseline and subsequent visits for both datasets, supporting their reliability. However, the Cronbach α decreases for the CODR dataset and increases for the centralized reviewed dataset. Correlations with MMSE are also higher across visits for the centralized reviewed dataset.

For CODR, item analysis revealed a decrease in item correlations, with the lowest for Spoken Language (ICC = 0.42). For the centralized reviewed dataset, item analysis remained consistent, with increases in ICCs (0.72 - 0.78) and Word Recall (0.60 - 0.64), and a decrease in Spoken Language (ICC = 0.62). For CODR, 10/11 items (90.9%) of the ADAS-Cog showed decrease in ICCs of > 0.02, compared to 4/11 items (36.4%) for the centralized reviewed dataset.

CONCLUSIONS

Results have important implications for clinical research, rater education and centralized data surveillance. The difference in ICCs between data sources demonstrates that centralized review of the ADAS-Cog can detect rater errors and increase reliability of the scale. Findings emphasize the value of centralized review in maintaining scale reliability across longitudinal studies, and suggest that targeted rater education and within-trial surveillance can improve data quality.

REFERENCES


DISCLOSURES AND CONTACT INFORMATION

A Khan is a full-time employee of NeuroCog Trials, Durham, NC, USA. (and has received support from National Institute of Mental Health; National Institute on Aging; I. Stroescu, V. Davis, T. Williamson and K. Budd McMahan are employees of Merck & Co., Inc., Kenilworth, NJ, USA. RSE Keele currently or in the past 3 years has received investigator-initiated research funding support from the Department of Veteran’s Affairs, Feinstein Institute for Medical Research, GlaxoSmithKline, National Institute of Mental Health, Novartis, Psychogenics, Research Foundation for Mental Illness, Inc., and the Singapore National Medical Research Council. He currently or in the past 3 years has received honoraria, served as a consultant, or advisory board member for Abbott, Alexza, Ames, Acura, Avanir/CereGene; BialyMed, Biogen IdeCer, Biometrics, Beurer, Boehringer-Ingehelm, Eli Lilly, EnVivo/PFIZER, GW Pharmaceuticals, Janovick, Lundbeck, Merck, Minerva Neurosciences, Inc., Mitsubishi, Novartis, NY State Office of Mental Health, Otsuka, Pfizer, Reva, Roche, SanofiAventis, Shire, Sunovion, Takeda, Taqayset, and the University of Texas South West Medical Center. Dr. Keele receives royalties from the BACS testing battery, the MATRICS Battery (BACS Symbol Coding) and the Virtual Reality Functional Capacity Assessment Tool (VRFACT). He is also a shareholder in NeuroCog Trials and Sengenix.

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DATASETS

ADAS-Cog Characteristics of First Recorded Visit by Group: Centralized Reviewed Dataset and CODR Dataset

<table>
<thead>
<tr>
<th>Dataset</th>
<th>ADAS-Cog Characteristics of First Recorded Visit by Group</th>
<th>Centralized Reviewed Dataset</th>
<th>CODR Dataset</th>
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