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Attaching Clinical Meaningfulness to CDR-SB Scores

Background

The Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) is the sole primary endpoint in most clinical trials of early symptomatic Alzheimer's Disease (AD) (Morris, 1993) and has been deployed as such in recent trials of monoclonal antibodies against beta amyloid that have received FDA approval (U.S. Food and Drug Administration, 2021). These approvals have put a renewed spotlight on what is meaningful change and measuring the rate of progression of disease. The CDR is not a tool that is commonly used in clinical practice, however, and there is some lack of clarity as to what relatively small differences in CDR-SB score changes between treatment and placebo arms in clinical trials translate to in terms of clinical meaningfulness for study participants and families.

Methods

To explore this, we examined the functional status of participants as measured by the Amsterdam Independent Activities of Daily Living (A-IADL) scale in trials where the CDR and the A-IADL scale were administered at the same visits (Sikkes, et al., 2012). Higher scores on both the CDR and A-IADL indicate higher impairment. We collated data from 7 secondary prevention and early symptomatic trials involving AD biomarker-positive participants.

Results

- A total of 6,452 pairs of CDR-SB and A-IADL scores were obtained, with CDR-SB scores ranging from 0-6 **(Table 1).** The mean CDR-SB score was 1.8 (SD = 1.96).
- **Figure 1** shows the relationship between the CDR-SB and the A-IADL total scores. The figure indicates a functional decline with each stepwise increase in CDR-SB score.
- In participants with a CDR-SB score of 1.5, there were no A-IADL items where the majority (i.e., ≥ 50%) of the sample reported difficulty. In contrast, in participants with a CDR-SB score of 2.5, the majority of the sample reported difficulty with the 7 A-IADL items below:
  - Look for important things at home
  - Learn to use new electronic devices
  - Deal with unexpected circumstances
  - Attempt to understand his/her paperwork
  - Find his/her keys
  - Work
  - Learn to do new things on the computer

Conclusions

As we approach the advent of approved FDA treatment for early symptomatic AD there is a growing need for real world data on the meaningfulness of the change on statistical analyses for what would constitute meaningful change. We believe the results presented showing the relationship between loss of function as a study participant progresses in the stages of their disease provide a more concrete, "real-world" understanding the association between CDR-SB scores and functional status in AD trial participants.

CDR-SB	CDR-SB	A-IADL Total Score (mean)	A-IADL Total Score (SD)
0.0	2624	0.2	1.5
0.5	529	1.2	3.3
1.0	324	3.2	5.7
1.5	307	4.7	6.3
2.0	304	8.9	9.3
2.5	302	13.1	13.6
3.0	334	17.8	14.6
3.5	367	21.9	15.7
4.0	371	27.7	17.4
4.5	269	33.0	18.2
5.0	335	42.9	19.8
5.5	156	44.9	19.6
6.0	230	51.5	20.5

Table 1: CDR-SB and Mean (SD) A-IADL Total Score Relationships

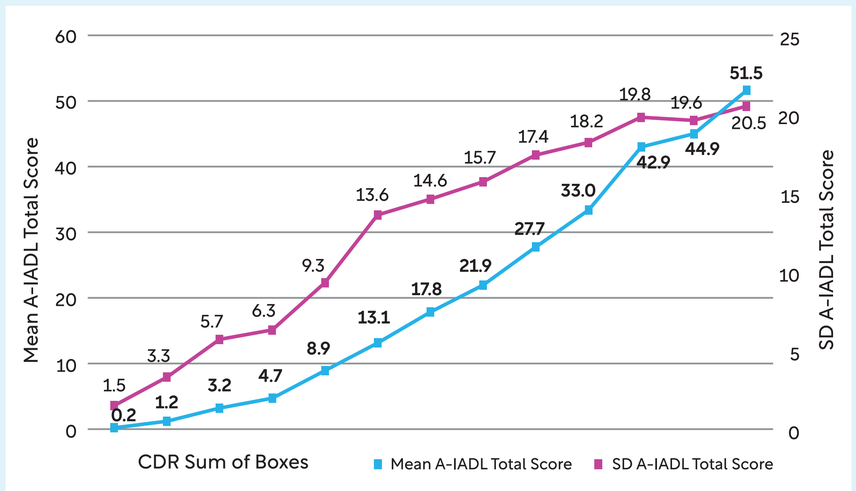

Figure 1: A-IADL Total Score as a Function of CDR-SB

References

Morris JC. The clinical dementia rating (CDR): current version and scoring rules. Neurology 1993;43:2412–4.

Sikkes SA, de Lange-de Klerk ES, Pijnenburg YA, et al. A new informant-based questionnaire for instrumental activities of daily living in dementia. Alzheimers Dement. 2012;8(6):536-43.

U.S. Food and Drug Administration (FDA). FDA grants accelerated approval for Alzheimer's drug. FDA News Release; 2021. Available from: https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug. Accessed November 14, 2021.