Exploring Discordant Data in Dementia Clinical Trials

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BACKGROUND

- We have anecdotally observed a number of discrepancies between the directionality of visit-to-visit changes between instruments such as the MMSE, ADAS-Cog and CDR in Alzheimer's dementia (AD) clinical trial data.
- While there is no expectation that all instruments need to move in one direction, clinically meaningful changes in opposite directions can, among other things, be a sign of scoring and/or administration errors in any of the affected instruments.
- In the current analysis, we explore:

  a) the extent to which discordances between the MMSE, ADAS-Cog and CDR changes are present in dementia clinical trial data

  b) whether any associations can be identified between the presence of between scale discordances and scoring and/or administration errors.

METHODS

- Blinded data were obtained from multi-national dementia clinical trials in early AD.
- Point change from prior visit was calculated for the MMSE, ADAS-Cog and CDR-SB.
- A literature review found that cut-offs for clinically meaningful changes were considered to be at least 4 points for the ADAS-Cog, 3 points for the MMSE and 1 point for the CDR-SB.
- Discordance was defined as occurring when at least 2 of the 3 instruments showed a clinically meaningful change, but the changes were in opposite directions.
- Additionally, we evaluated data resulting from review, by experienced, independent clinicians of the scale worksheets and audio recordings that identified the presence of administration and/or scoring errors.
- Descriptive statistics as well as logistic regression analyses were used to address our questions.

RESULTS

- Data were collected from 4,892 randomized subjects.
- Visit-to-visit discordances were identified in 1,732 out of 15,321(11.30%) collected visits.
- Discordances were significantly less likely at baseline than after randomization (OR=0.62; CI=0.55-0.0.70) (Figure 1).
- The presence of baseline discordances significantly increased the odds of post-baseline discordances (OR = 1.70; CI=1.36-2.12) (Figure 2).
- No association between the presence of discordances and administration or scoring errors was identified (Figure 3).

FIGURE 1: PRESENCE OF VISIT-TO-VISIT DISCORDANCES AT BASELINE AND AFTER RANDOMIZATION

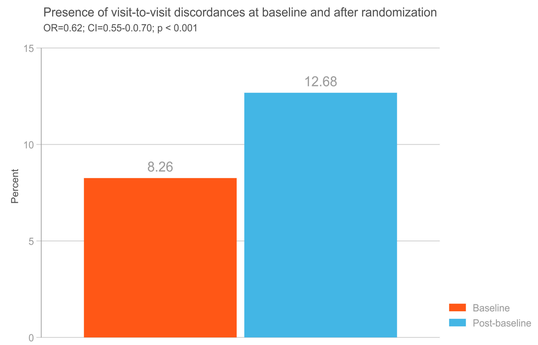


FIGURE 2: SUBJECTS AFFECTED BY THE PRESENCE OF VISIT-TO VISIT DISCORDANCES AFTER RANDOMIZATION BY THE PRESENCE OF BASELINE DISCORDANCE

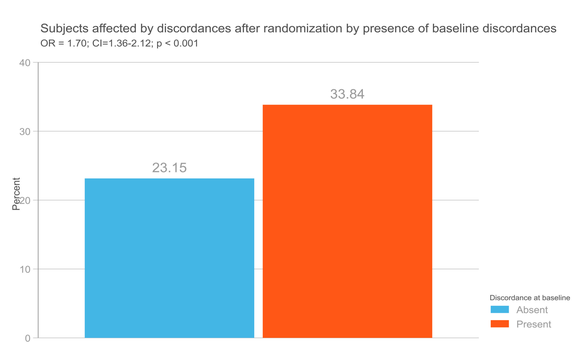
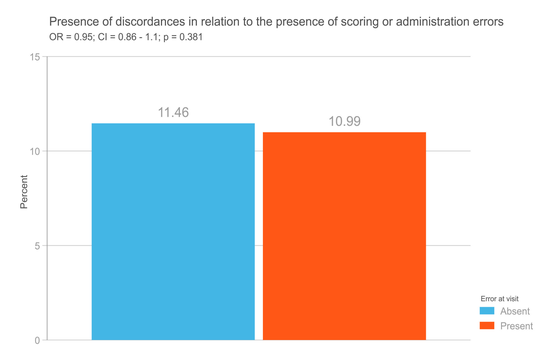


FIGURE 3: RELATIONSHIP BETWEEN THE PRESENCE OF VISIT-TO-VISIT DISCORDANCES AND THE PRESENCE OF SCORING AND/OR ADMINISTRATION ERRORS



DISCUSSION

- We have identified over 11% of study visits affected by clinically meaningful discordances between the visit-to-visit changes between the MMSE, ADAS-Cog and CDR-SB.
- Despite the expected lower presence of baseline than post-baseline discordances, discordances at baseline affected over 8% of randomized subjects.
- The lack of association between the discordances and administration or scoring errors is surprising and we plan further analyses to understand this phenomenon better.

REFERENCES

- Andrews, J. Scott; Desai, Urvi; Kirson, Noam Y.; Zichlin, Miriam L.; Ball, Daniel E.; Matthews, Brandy R. (2019): Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. In Alzheimer's & dementia (New York, N. Y.), pp. 354–363. DOI: 10.1016/j.trci.2019.06.005.

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