Exploring Discordant Data in Dementia Clinical Trials

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BACKGROUND

- We have observed numerous apparent inconsistencies in direction of scale (eg – MMSE, ADAS-Cog and CDR) change between visits across multiple dementia clinical trials.
- While not all instruments are expected to change to the same degree, clinically meaningful changes in opposite directions may signal scoring and/or administration errors in one or more scales.
- In this analysis, we explore:

  a) the extent to which such discordances between the MMSE, ADAS-Cog and CDR occur in dementia clinical trials

  b) whether any associations between the presence of such discordances and scoring and/or administration errors exist

METHOD

- Blinded data were obtained from multi-national dementia clinical trials in early AD.
- Visit-to-visit point change was calculated for the MMSE, ADAS-Cog and CDR-sb.
- Clinically meaningful changes were defined based on literature review as:
  - ≥ 4 points for the ADAS-Cog
  - 3 points for the MMSE
  - 1 point for the CDR-sb
- We defined discordance occurring when at least 2 of 3 instruments showed clinically meaningful change, but in opposite directions.
- We also evaluated data from the corresponding Endpoint Quality reviews of both the worksheet and audio recordings of these assessments.
  - These were performed by calibrated, independent Clinicians and assessed for the presence of any administration and/or scoring errors
- Descriptive statistics and logistic regression analyses were used to address our questions.

RESULTS

- Data were collected from 5,452 randomized subjects.
- Visit-to-visit discordances were identified in 2,262 out of 20,127 (11.24%) collected visits.
- Discordances were significantly less likely at baseline than after randomization (OR=0.57; CI=0.54-0.0.61) [Figure 1].
- The presence of baseline discordances significantly increased the odds of post-baseline discordances (OR = 1.41; CI=1.14-1.75) [Figure 2].
- No association between the presence of discordances and administration or scoring errors was identified (OR = 1.00; CI=0.92-1.10) [Figure 3].

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

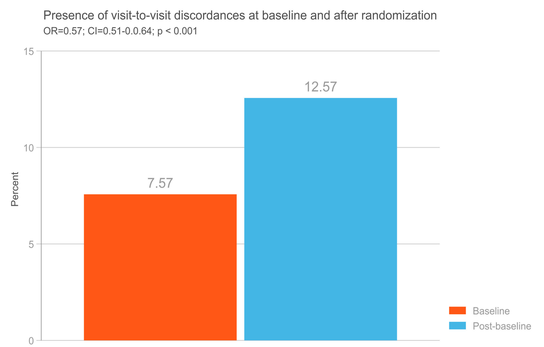


FIGURE 2: SUBJECTS AFFECTED BY DISCORDANCES AFTER RANDOMIZATION BY PRESENCE OF BASELINE DISCORDANCES

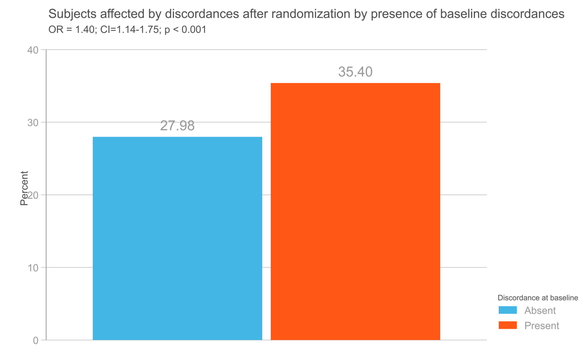
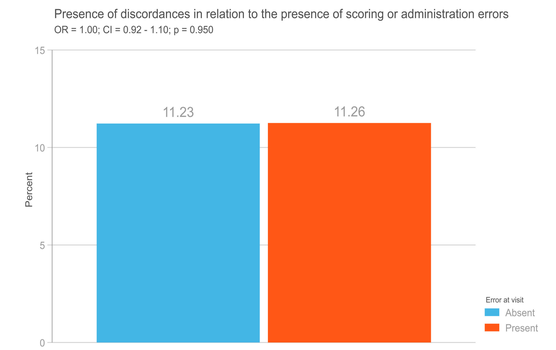


FIGURE 3: PRESENCE OF DISCORDANCES IN RELATION TO THE PRESENCE OF SCORING OR ADMINISTRATION ERRORS



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 almost 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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