Impact of Protocol Design on Between Scale Discrepancies in Early AD Clinical Trials

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BACKGROUND

- We previously presented research showing the impact of protocol design on the MMSE changes observed in the screening period.
- Protocols requiring that inclusion criteria be met at Screening alone had significantly more large MMSE changes between Screening and Baseline than did protocols where the criteria needed to be met at both Screening and Baseline. [Kott and Miller, 2020]
- In the current analysis we explore the impact of protocol design on the presence of between scale change discrepancies at Baseline and 6 months after randomization.

METHODS

- Data were pulled from multi-national clinical trials in early AD where MMSE and ADAS-Cog and/or CDR were collected at Screening, Baseline and 6 months after Baseline.
- Subjects were categorized into 2 groups depending on whether inclusion criteria were required at Screening alone or at Screening and Baseline.
- We defined discordance as occurring when at least 2 of the 3 instruments showed a clinically meaningful change from the prior visit and the changes were in opposite directions.
- Per a literature review, clinically meaningful change was considered to be at least 4 points for the ADAS-Cog, 3 points for the MMSE and 1 point for the CDR-SB.
- Chi-square test was used to compare the distribution of discordances between the protocols at Baseline and at month 6.

RESULTS

- Our dataset consisted of 4,237 subjects with data available from Screening, Baseline and month 6.
- At Baseline, we saw significantly more instances of discordance from Screening in studies requiring criteria be met at Screening alone (5%) vs 2% when the requirement needed to be met at both Screen and Baseline (chi2 = 12.5, P < 0.001) (Figure 1).
- At month 6, no difference between the protocol types was identified – (12.2% vs. 12.4%, chi2 = 0.01, p = 0.912) (Figure 2).

FIGURE 1: PRESENCE OF VISIT-TO-VISIT DISCORDANCES AT BASELINE BY PROTOCOL TYPE

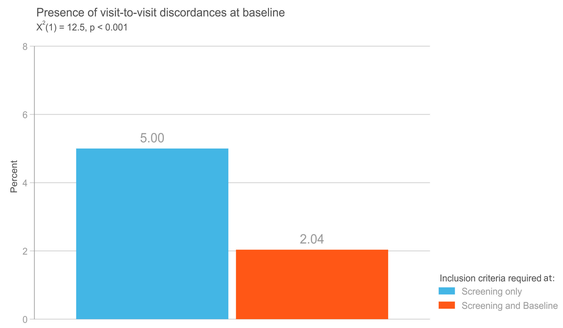
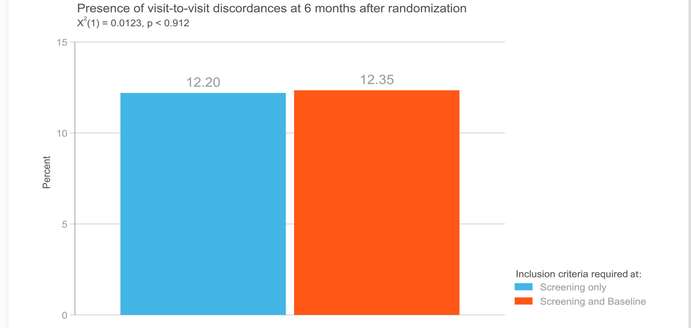


FIGURE 2: PRESENCE OF VISIT-TO-VISIT DISCORDANCES AT MONTH 6 AFTER RANDOMIZATION BY PROTOCOL TYPE



DISCUSSION

- Our analyses indicate a significant impact of protocol design on the presence of between scale change discrepancies.
- Protocols requiring criteria be met at Screening only had a significantly increased number of discordances at Baseline but this difference disappeared by month 6.
- Among the potential explanations for such between scale discordances, score manipulation to comply with inclusion criteria needs to be considered.
- These findings should be considered when designing protocol inclusion criteria.
- Further research is necessary to understand the impact of these discrepancies on drug-placebo separation.

REFERENCES

- Kott, Alan; Miller, David (2020): The impact of protocol design on MMSE changes in the screening period.

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