## RESULTS

### ADAS-Cog Visit-to-Visit Change

- **Figure 2:** Changes in ADAS-Cog total score from (a) baseline to 6 months (± 30 days), (b) baseline to 12 months (± 30 days), and (c) baseline to 18 months (± 30 days). One implausible score change of 51 was removed from (a) baseline to 6 months.

- **Figure 3:** Mean change in ADAS-Cog total score from baseline by MMSE total score at baseline for visits (a) 4 months (± 30 days) from baseline; (b) 12 months (± 30 days) from baseline.

### ADAS-Cog Change from Baseline

- **Figure 4:** Change in ADAS-Cog total score from (a) baseline to 6 months (± 30 days), (b) baseline to 12 months (± 30 days), and (c) baseline to 18 months (± 30 days). One implausible score change of 51 was removed from (a) baseline to 6 months.

- **Figure 5:** MMSE total scores at baseline for each study.

### MMSE Baseline Distributions

- **Table 1:** Study information for studies in the CODR database used in analyses.

### CONCLUSIONS

Large variability and extreme outliers in visit-to-visit ADAS-Cog change scores, including those of a biologically implausible magnitude, were fairly common, suggesting significant error variance. Overall change on the ADAS-Cog over time was somewhat less than expected based upon published data. The percent of subjects who failed to worsen decreased over time with 40 percent of subjects not worsening by more than one point at 18 months. This is markedly less cognitive decline on placebo than previous estimates and may therefore reflect a publication bias whereby failed trials are less likely to be reported in the peer-reviewed literature. Change on the ADAS-Cog was strongly dependent upon baseline MMSE, and visit-to-visit variability on the ADAS-Cog was fairly high. These findings suggest that accurate subject selection is critical for obtaining placebo decline on the ADAS-Cog, and that in-study quality control methodologies should be further explored for efficacy in reducing error variance.

---

### METHODS

Baseline visits were determined using the baseline flag variable in the CODR database. Four studies had baseline MMSE scores at separate visits from ADAS-Cog baseline scores (studies 1056, 1057, 1135, and 1142). For these studies, the baseline visit was determined by scale (e.g., MMSE at visit one and ADAS-Cog at visit two). Additionally, four studies (1056, 1057, 1058, and 1138) had baseline flags for additional visits (e.g., baseline flag at visit two with some subjects having a baseline flag at visit three). These were not included as baseline visits as they occurred rarely (<4 percent of subjects per study) and were likely data entry errors or protocol deviations.

We examined baseline MMSE distributions to examine variability of baseline cognitive impairment. We analyzed overall visit-to-visit change in ADAS-Cog total score for all visits ≤ 90 days apart. We used a kurtosis range = -1.06 to -0.12).

**Table 1.** MMSE Baseline scores ranged from 10 – 30. Distributions of these scores for each study are shown (Table 1), with a total of 3,319 subjects across 26,012 visits.

- **Study**
  - **Study Length (months)**
  - **Baseline Visit**
  - **Baseline Visit for ADAS-Cog**
  - **Study**
  - **Baseline Visit**
  - **Study**
  - **Baseline Visit**
  - **Study**
  - **Baseline Visit**
  - **Study**
  - **Baseline Visit**
  - **Study**
  - **Baseline Visit**
  - **Study**
  - **Baseline Visit**

---

### REFERENCES

- **Randolph, C**...
- **ADAS-Cog Visit-to-Visit Change**

**Figure 2.** Visit-to-visit change in ADAS-Cog total score for visits (a) 2 weeks apart.

**Figure 3.** Mean change in ADAS-Cog total score from baseline by MMSE total score at baseline for visits (a) 4 months (± 30 days) from baseline; (b) 12 months (± 30 days) from baseline.

**Figure 4.** Change in ADAS-Cog total score from (a) baseline to 6 months (± 30 days), (b) baseline to 12 months (± 30 days), and (c) baseline to 18 months (± 30 days). One implausible score change of 51 was removed from (a) baseline to 6 months.