# High Variability and Lack of Change on the ADAS-Cog: Placebo Analyses of the CODR Database

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## INTRODUCTION

The Alzheimer's Disease Assessment Scale-Cognitive Section (ADAS-Cog)[1] is the most commonly used primary neurocognitive endpoint in clinical trials of mild-moderate Alzheimer's disease. However, concerns have been raised regarding the lack of sensitivity of this instrument in mild disease and with respect to the magnitude of error variance[2]. Lack of cognitive decline in placebo subjects has been cited as a reason for recent clinical trial failures[3,4]. Further, frequent errors in administration and scoring can increase variability and decrease reliability of ADAS-Cog placebo change scores[2]. Reliable assessment of cognitive decline on placebo is essential to demonstrating treatment efficacy, particularly with treatments designed only to slow cognitive decline[3,4].

In an effort to drive advances in Alzheimer's disease therapeutic development, the Critical Path (C-Path) initiative created the C-Path Online Data Repository (CODR) that contains data from the placebo arms of over 20 clinical trials.

We analyzed the CODR database to explore variability and change in ADAS-Cog scores as a function of time and baseline MMSE score, to further inform clinical trial design for this population. The goals of this analysis were to 1) determine how much variability is seen in ADAS-Cog placebo scores in the CODR database, 2) assess how well inclusion MMSE total scores predict changes in ADAS-Cog scores over time, and 3) assess the variability and degree of cognitive decline in placebo subjects on the ADAS-Cog across 14 trials in the CODR database.

## METHODS

There were a total of 24 studies in the CODR database containing only data from subjects in the placebo arm. We eliminated trials of less than six months duration (n = 2), open label extension studies (n = 2) and trials that did not include the ADAS-Cog as an endpoint (n = 6). There were 14 studies remaining (see Table 1), with a total of 3,939 subjects across 26,123 visits.

The ADAS-Cog and MMSE were administered in all but one study (Study 1141).

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 (<14 percent of subjects per study) and were likely data entry errors or protocol deviations.

To consistently compare all studies, ADAS-Cog total scores were calculated as the sum of the common 11 items. Time elapsed from baseline was calculated as visit day minus baseline day. Changes in scores were calculated as visit total score minus baseline total score, with a positive score change indicating worsening symptoms.

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 in 14 studies to quantify variability. A test-retest correlation was calculated as Pearson's r correlation between a subject's ADAS-Cog total score at time one compared to time two for all visits ≤ 90 days apart.

Changes in ADAS-Cog total scores over time were also analyzed as baseline to 6-month (± 30 days) change, baseline to 12-month (± 30 days) change, and baseline to 18-month (± 30 days) change.

Change scores over time were analyzed as a function of baseline MMSE total score in 13 studies.

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

| Study# | Study Length (months)[a] | Baseline Visit # for ADAS-Cog | Baseline Visit # for MMSE | # Subject Screened |
|---|---|---|---|---|
| 1055 | 12.8 | 10100 | 10100 | 135 |
| 1056 | 14.0 | 20 | 10 | 493 |
| 1057 | 16.7 | 20 | 10 | 499 |
| 1058 | 7.0 | 30 | 30 | 166 |
| 1105 | 21.6 | 2 | 2 | 326 |
| 1131 | 6.0 | -1 | -1 | 57 |
| 1132 | 15.5 | 1 | 1 | 412 |
| 1133 | 8.4 | 1 | 1 | 162 |
| 1135 | 8.4 | 1 | 0 | 274 |
| 1137 | 7.4 | 2 | 2 | 213 |
| 1138 | 7.6 | 2 | 2 | 199 |
| 1140 | 6.2 | 1 | 1 | 137 |
| 1141[b] | 26.5 | 2 | N/A | 465 |
| 1142 | 28.1 | 2 | 1 | 401 |

[a]Calculated from the maximum study day in database
[b]MMSE not administered in this study

## RESULTS

### MMSE Baseline Distributions

MMSE total scores at baseline ranged from 10 – 30. Distributions of these scores for some studies were relatively normal, while others were negatively skewed with fewer subjects enrolled at lower MMSE ranges (Fig. 1, skewness range = -0.60 to -0.14, kurtosis range = -1.06 to -0.12).

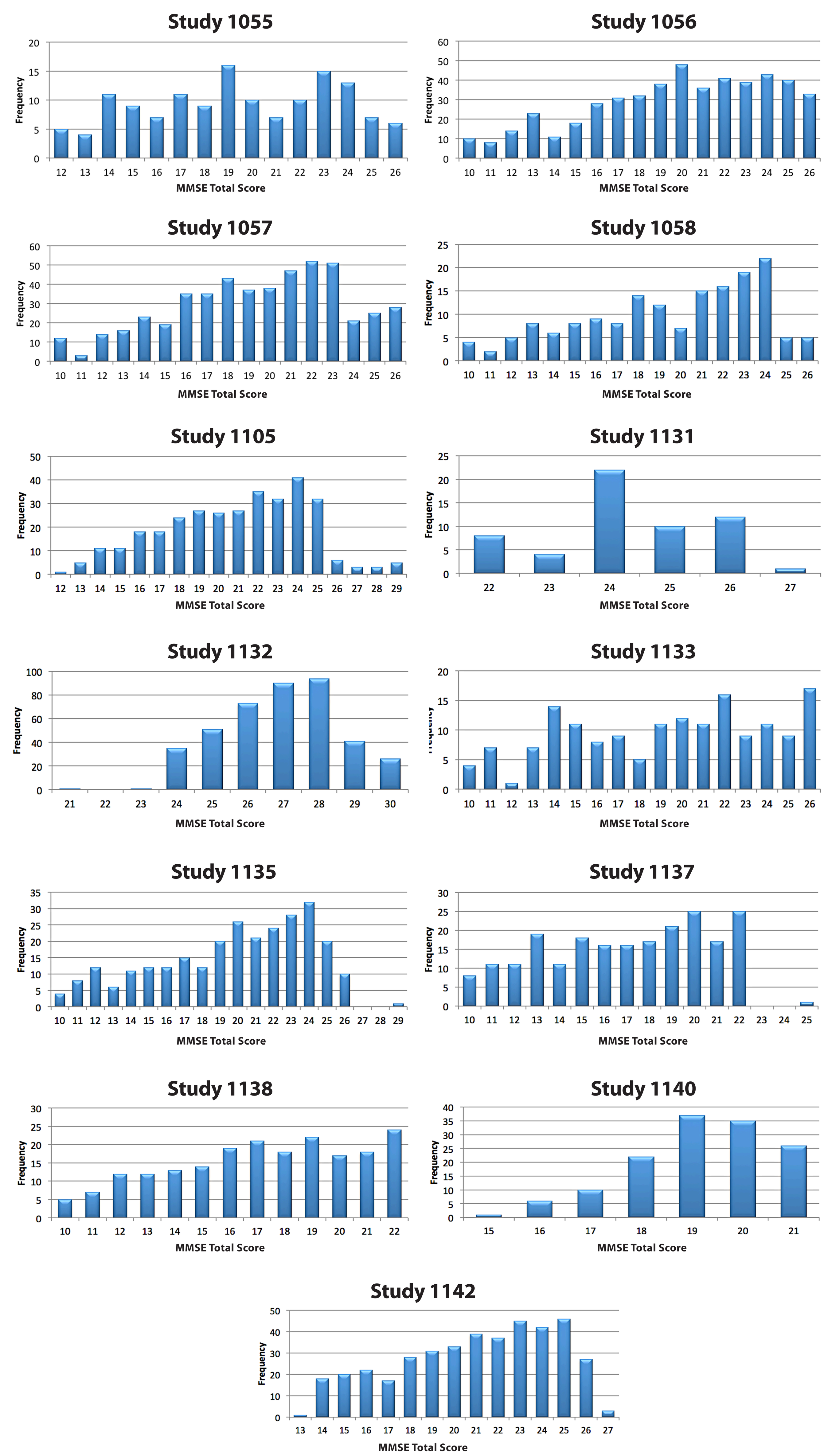


**Figure 1.** MMSE total scores at baseline for each study

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

Mean ADAS-Cog scores at baseline ranged from 9.3 (± 5.2 SD) to 27.8 (± 9.6 SD). The visit-to-visit test-retest correlation for the ADAS-Cog was 0.91.

Average visit-to-visit change on the ADAS-Cog was 0.5 (± 5.2) ranging from -35 to 40; 40 percent of subjects improved during the 90-day visit window (Fig. 2).

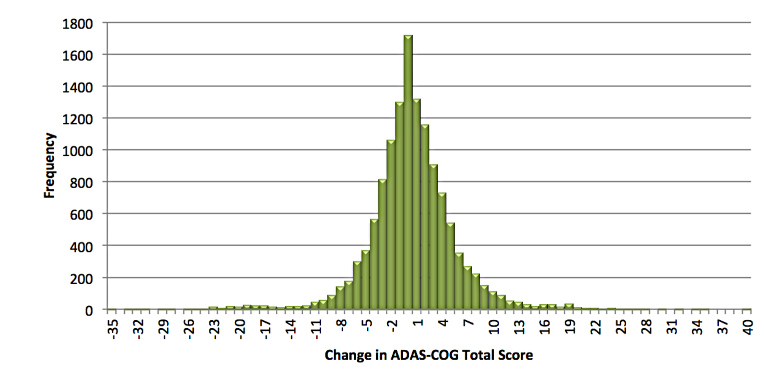


**Figure 2.** Visit-to-visit change in ADAS-Cog total score for visits ≤ 90 days apart.

### ADAS-Cog Change from Baseline

Average change from baseline was 1.0 (± 5.7), 2.6 (± 7.1), and 3.9 (± 8.0) for 6, 12 and 18 months, respectively; 42 percent, 34 percent and 32 percent of subjects improved, respectively (Fig. 3). 58 percent, 49 percent and 45 percent of subjects did not worsen by more than 1 point, respectively.

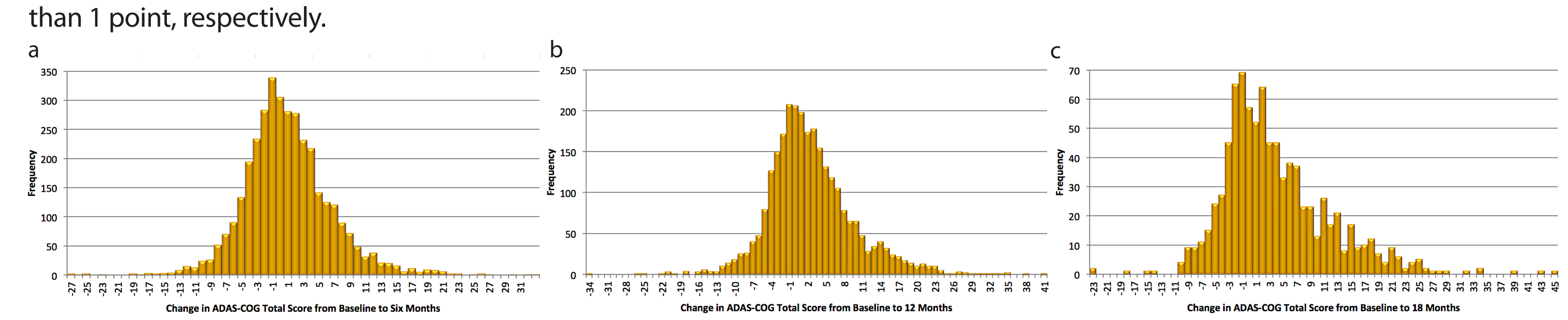


**Figure 3.** Change in ADAS-Cog total score from (a) baseline to 6 months (± 30 days), (b) baseline to 12 months (± 30 days), and (c) baseline to 18 months (± 30 days). One implausible score change of 51 was removed from (a) baseline to 6 months.

### ADAS-Cog Change from Baseline as a function of MMSE Score

MMSE was a significant predictor of change in ADAS-Cog score from baseline to 6, 12, and 18 months ($\beta$ = -0.18, -0.22, and -0.27, all p's < .05) with higher baseline MMSE scores associated with less decline over time (Fig. 4).

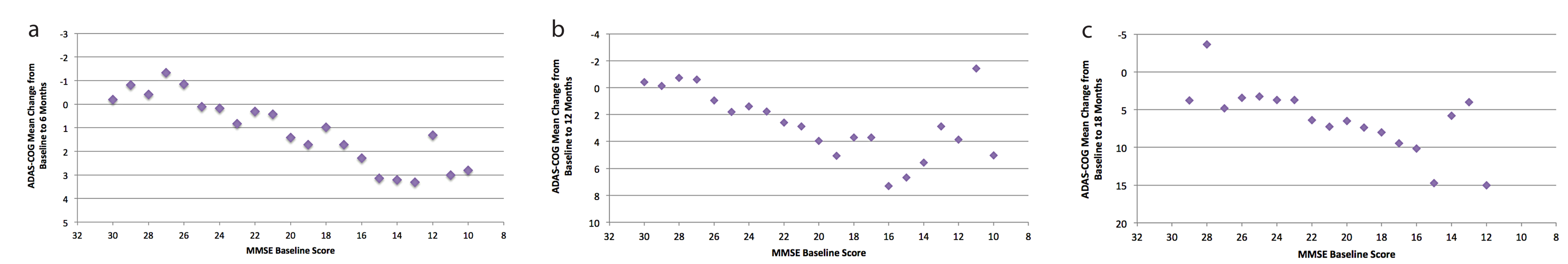


**Figure 4.** Mean change in ADAS-Cog total score from baseline by MMSE total score at baseline for visits (a) 6 months (± 30 days) from baseline, (b) 12 months (± 30 days) from baseline, and (c) 18 months (± 30 days) from baseline.

## 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 45 percent of subjects not worsening by more than one point at 18 months. This is markedly less cognitive decline on placebo than previous estimates[3] 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.

## REFERENCES

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**Conflict of Interest.** One or more authors report potential conflicts which are described in the program.

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