Appendix 2. Approximating linear clinical decline in MCI over time.

A composite score measuring the disease status based on ADAS-cog, MMSE, and CDR-SB at time *t* may be expressed as

$$S(t) = \sum_{i=1}^{12} a_i A_i(t) + \sum_{i=1}^{7} b_i B_i(t) + \sum_{i=1}^{6} c_i C_i(t) \tag{1.1}$$

where $A_i(t)$, $B_i(t)$ and $C_i(t)$ are item scores at time t corresponding to items from ADAS-cog, reversed MMSE, and CDR-SB, respectively. The MMSE scores were reversed in order to have higher scores correspond to more impairment across all items. For example, if the maximum score for a MMSE item M_i is 5, then $B_i(t)$ is calculated as $(5\text{-}M_i(t))$.

We were more interested in a simple functional form for modeling the short-term decline across early AD. The change from baseline of $S(t)$ can be expressed as the following Taylor series.

$$\Delta S(t) = S(t) - S(t_0) = S'(t_0)(t - t_0) + \frac{1}{2!} S''(t_0)(t - t_0)^2 + \cdots \tag{1.2}$$

where t_0 is the time at baseline and the notation Δ represents the change from baseline at time *t*. Although the true functional form of short-term decline is unknown, the plot of mean change from baseline for various scores overtime suggested a strong linear trend over a 24-month period (Fig. 2.1). Therefore, the linear component of $\Delta S(t)$ would be a good approximation of ΔS(t). An approximate model keeping the second and higher-order terms in Taylor expansion might fit the observed data better. However, the robustness and the predictive value of the fitted model with higher order terms might be discounted. The modeling experiences have indicated that a linear approximation is usually sufficient in practice unless the data suggests a strong nonlinear trend. Therefore, it would be appropriate to drop the second and higher-order items from function (1.2) and thus the change from baseline at any time *t* is approximately

$$\Delta S(t) = \sum_{i=1}^{12} a_i \Delta A_i(t) + \sum_{i=1}^{7} b_i \Delta B_i(t) + \sum_{i=1}^{6} c_i \Delta C_i(t) = S'(t_0)(t - t_0) \tag{1.3}$$

Dividing by $S'(t_0)$ on both sides of equation (1.3), we would have

$$(t-t_0)=\sum_{i=1}^{12}(a_i/S^{'}(t_0))\Delta A_i(t)+\sum_{i=1}^{7}(b_i/S^{'}(t_0))\Delta B_i(t)+\sum_{i=1}^{6}(c_i/S^{'}(t_0))\Delta C_i(t). \quad (1.4)$$

or

$$(t-t_0)=\sum_{i=1}^{12}d_i\Delta A_i(t)+\sum_{i=1}^{7}e_i\Delta B_i(t)+\sum_{i=1}^{6}f_i\Delta C_i(t). \quad (1.5)$$

where $d_i = a_i/S'(t_0)$, $e_i = b_i/S'(t_0)$, and $f_i = c_i/S'(t_0)$.

The linear clinical decline equation (1.5) was used to model the clinical decline. The time at the left side of the equation is the duration of decline and can be regarded as a surrogate response variable for measuring rescaled decline such that the decline rate is 1. The right side of the equation is a weighted linear combination of predictor variables or decline of items measuring cognitive and global functions. This linear clinical decline model will be fitted using PLS regression to identify items more sensitive to clinical decline and find appropriate weights for an optimal combination.