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LETTER

Frequent self-assessments in ALS Clinical Trials: worthwhile or an unnecessary burden for patients?

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Dear Editor,

With interest I have read the article published by Rutkove and colleagues on frequent at-home self-assessment for clinical trials in amyotrophic lateral sclerosis (ALS).[1] An important consideration is to determine the optimal monitoring frequency (e.g., daily, weekly, or monthly) in order to balance the gain in information with the increase in patient-burden. The authors address this question by performing sample size calculations to detect a 30% reduction in the progression rate for a 9-month randomized clinical trial. The authors report a surprising 73.3% reduction in sample size (from 274/arm to 73/arm) if monitoring frequency for the ALS functional rating scale (ALSFRS-R) would be increased from monthly to weekly. It seems, however, that the calculation may have been over-optimistic and the reported reductions may need to be interpreted with caution.

Longitudinal ALSFRS-R decline is classically evaluated using linear mixed effects models, where the model can be defined as:

$$\begin{aligned} \text{ALSFRS}-R_{ij} &= \beta_{0i} + \beta_{1i}\cdot \text{Time}_j + \varepsilon_{ij} \\ \beta_{0i} &= \beta_0 + \mu_{0i} \\ \beta_{1i} &= \beta_1 + \mu_{1i} \end{aligned}$$

where $\varepsilon_{ij} \sim \text{N}\left(0,\sigma_\varepsilon^2\right)$ and $\begin{matrix}\mu_{0i}\\ \mu_{1i}\end{matrix} \sim \text{N}\left(\begin{matrix}0\\0\end{matrix}, \begin{bmatrix}\sigma_{\mu_0}^2 & \rho\sigma_{\mu_0}\sigma_{\mu_1}\\ \rho\sigma_{\mu_0}\sigma_{\mu_1} & \sigma_{\mu_1}^2\end{bmatrix}\right)$.

In this model, β_{0i} and β_{1i} are the patient-specific baseline score and monthly rate of decline, respectively. During a clinical trial, we are primarily interested in the reduction of β_1 or the population-average rate of decline. The sample size to detect a reduction in β_1 depends primarily on (1) the absolute reduction Δ, (2) the within-patient variance (σ_ε^2), and (3) the between-patient variance ($\sigma_{\mu_1}^2$).[2] The required sample size is given by:

$$n/arm = 2\times\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \times \frac{\sigma_{\mu_1}^2 + \frac{\sigma_\varepsilon^2}{\sum\left(Time_i-\overline{Time}\right)^2}}{\Delta^2}$$

The term $\sum\left(Time_i-\overline{Time}\right)^2$ reflects the monitoring frequency; if the monitoring frequency is increased, the within-patient variance is reduced, while the between-patient variance remains unaffected (as can also be observed in the article's **Figure 2**). In fact, if the monitoring frequency is infinitely frequent, the sample size formula reduces to:

$$n/arm = 2\times\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \times \frac{\sigma_{\mu_1}^2}{\Delta^2}$$

The between-patient variance plays, therefore, a decisive role in longitudinal sample size calculations and, in case of the ALSFRS-R, the benefit of frequent monitoring is relatively small. For example, using the PRO-ACT database ($\beta_1 = -1.05$, $\sigma_{\mu_1}^2 = 0.57$, $\sigma_\varepsilon^2 = 4.76$, $\Delta = 0.31$), 133 patients/arm would be required for monthly monitoring, which reduces to 125 (−6.5%) for weekly monitoring or 122 (−9.1%) when monitoring infinitely frequent. Alternatively, using a similar cohort as reported by the authors ($\beta_1 = -0.59$, $\sigma_{\mu_1}^2 = 0.39$, $\sigma_\varepsilon^2 = 1.72$, $\Delta = 0.18$),[3] sample size reduces from 274 to 264 patients/arm (−3.6%) when monitoring weekly rather than monthly. The benefit of frequent ALSFRS-R monitoring may, therefore, be limited and not outweigh the increased patient burden, which is important to consider for future clinical trials.

Conflict of Interest

The author has no conflict of interest to disclose.

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