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REPLY TO LETTER

Reply to: Frequent self-assessments in ALS clinical trials: Worthwhile or an unnecessary burden?

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Dear Editor,

We appreciate Dr. van Eijk's letter,[1] and we agree: using a linear mixed effects model, the standard approach for ALS clinical trials, incorporates several features, including the absolute reduction in a given marker, its within-subject variance, and its between-subject variance. Similarly, we agree that, theoretically, the major impact of frequent measurements would be to improve the accuracy of the slope estimation for a given measure in any individual. And, indeed, it is a straightforward procedure to model this by taking the frequent sampling to its theoretical limit. We have full confidence in Dr. van Eijk's analysis of the PROACT database showing only modest improvements in sample size in the ALS functional rating scale-revised (ALSFRS-R) with frequent sampling.

The fault with this line of reasoning, however, is that the linear mixed effects model is just that: a model. It is a model built on a standard clinical trial design, including a fixed number of infrequent measurements made on a relatively large number of individuals. It also assumes that between-subject variance and mean slope will not be affected by frequent sampling. This assumption is likely reasonable in large data sets where noise in individual patient measurements will, on average, not impact the distribution of trajectories across the entire group. However, with a smaller sample, a noisy measure with respect to within-subject variance can also impact between-subject variance and, consequently, the mean slope as well. Our study[2] clearly shows these effects, where ALSFRS-R slope standard deviation drops from 0.041 to just 0.018 points/month, with an accompanying increase in the mean slope. Perhaps no measure demonstrates this better than right hand grip dynamometry, on which we had the most data. Here within-subject standard deviation decreased by 45% and between-subject standard deviation decreased by 37% and the mean slope increased by 22%, comparing monthly to daily measurements.

Nevertheless, we do appreciate Dr. van Eijk's letter because it does highlight two points in our article that we

under-appreciated ourselves. First, the marked improvements in ALSFRS-R sample sizes may in part be due to a higher degree of noise in this measure in our study than usual given that the subjects were completing it independently. Second, while we did discuss the improvement in individual slope estimation, we neglected to highlight the fact that better estimation of slopes can actually have the unexpected effect of reducing between-patient variance and improving estimation of mean slope as well.

Conflict of Interest

Dr. Rutkove holds equity in Myolex, Inc, (the company that produces the Skulpt Scanner used in this study), has served on its board of directors, has received consulting income from the company, and is named as an inventor on patents owned or licensed to Myolex, Inc.

References

1. van Eijk R. Frequent self-assessments in ALS clinical trials: worthwhile or an unnecessary burden for patients? Ann Clin Transl Neurol 2020.
2. Rutkove SB, Narayanaswami P, Berisha V, et al. Improved ALS clinical trials through frequent at-home self-assessment: a proof of concept study. Ann Clin Transl Neurol 2020;7:1148–1157.

