



Longitudinal Analysis of Individual Disease Progression in a Clinical Trial-Eligible ALS Cohort – Comparing Digital Speech Biomarkers to the ALSFRS-R

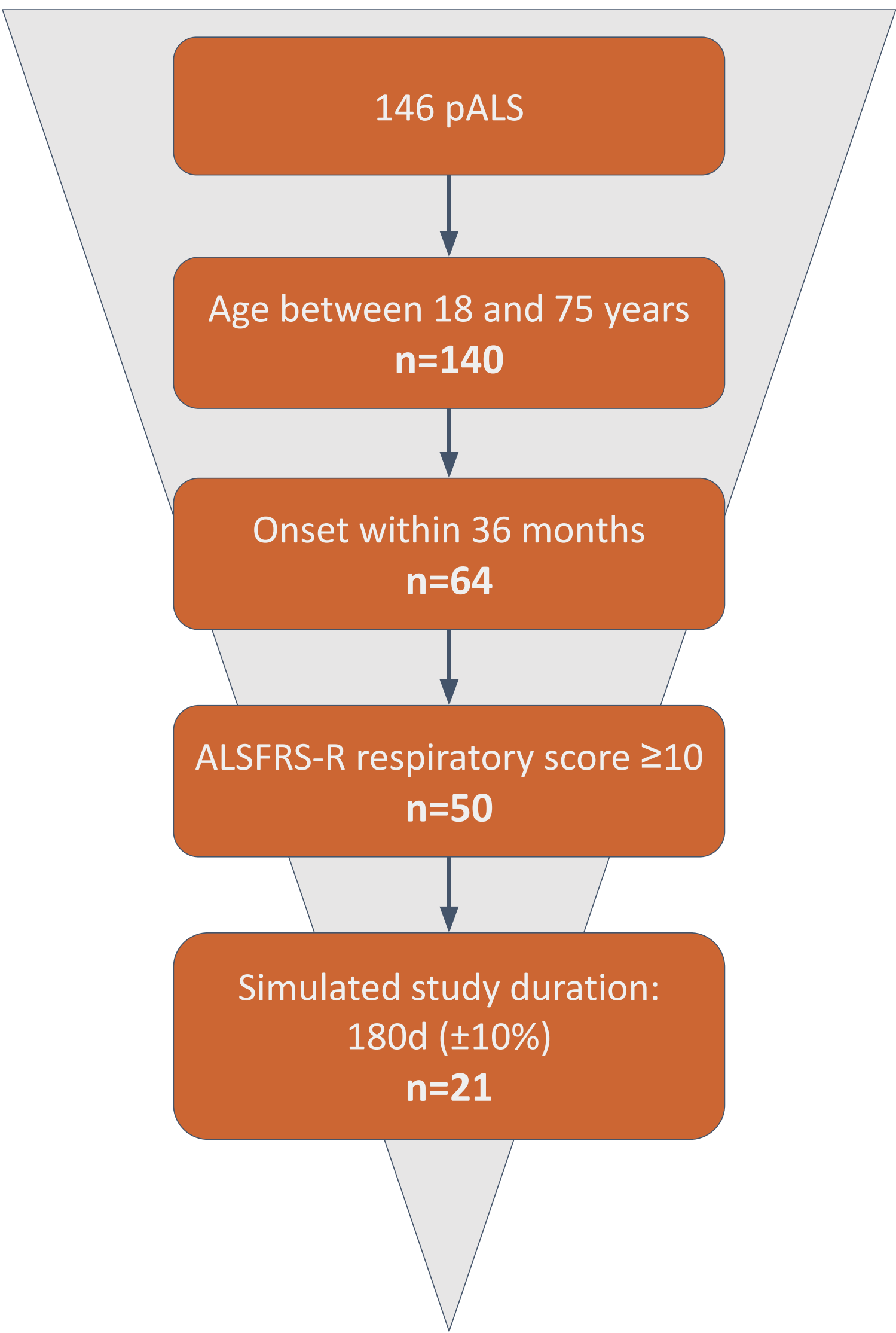
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Introduction

- **Digital health technologies (DHT)** have become increasingly relevant for enhancing clinical trials [1,2]
- We demonstrate the **utility and sensitivity of remotely recorded speech markers** to characterize speech deterioration compared to the ALS functional rating scale - revised (ALSFRS-R)
- Challenges in ALS research include:
 - Heterogeneity of disease progression
 - Differences trial designs and natural history studies
- To address these challenges, we focus on:
 - Longitudinal **rate of change at the individual level** instead of group level effects
 - Studying a **subgroup of a large natural history study** that meets typical **clinical trial eligibility criteria**

Methods

- **146 people with ALS** participated in a **self-administered speech assessment** using a web-based multimodal dialog system
- Recordings of the Bamboo reading passage were used to extract **speaking rate and CTA** (canonical timing alignment, a measure of timing and intelligibility)



- Participants were selected to emulate typical clinical trial eligibility criteria:
 - Age between 18 and 75 years
 - Symptom onset within 36 months prior to study enrollment
 - ALSFRS-R respiratory subdomain score (Q10-12) ≥10 (surrogate for FVC/SVC)
- Participants with sufficient data for a simulated study duration of 180 days (±10%) were included
- **21 participants** remained (11 female; 5 with bulbar onset; mean age 62.9 ± 7.2 years)

Figure 1. Participant selection.

- Linear regression was performed to estimate the **rate of change from baseline for each participant** for the **ALSFRS-R speech sub score** (ranges from 0 to 4), **speaking rate and CTA**
- To account for **practice effects**, mean slopes of the speech measures for an age and sex matched healthy control (HC) cohort were estimated and subtracted from the pALS' slopes (assumption: equal practice effect across HC and pALS)

References

[1] Kunkoski, E., Saha, A., & Kam, M. M. (2025, April). FDA Perspective on the Importance of Digital Health Technologies in Clinical Trials. In JAMA Health Forum (Vol. 6, No. 4, pp. e250165-e250165). American Medical Association.

[2] Rosa, C., Marsch, L. A., Winstanley, E. L., Brunner, M., & Campbell, A. N. (2021). Using digital technologies in clinical trials: current and future applications. Contemporary clinical trials, 100, 106219.

Results

- 35 participants fulfilled the eligibility criteria, and 21 (5 with bulbar onset) had measurements over a period of 180 days
- Mean number of sessions per participant: 15.3 (±9.0)
- **ALSFRS-R speech** score showed a **decline for only four participants** (one significant at p<0.05)
- **Speaking rate** showed a **significant decline for 11 participants** after adjusting for practice effects (mean HC slope: 2.1 words per minute (WPM)/month)
- **CTA** showed a **significant decline for six participants** after adjusting for practice effects (mean HC slope: 0.01%/month)

Measure	Participants with significant decline (p<0.05)	Mean rate of change (adjusted)
ALSFRS-R speech	1	-0.04 points/month
Speaking rate	11	-3.89 WPM/month
CTA	6	-0.85 %points/month

Table 1. Number of participants with significant decline (individual level) and average rate of change (group level).

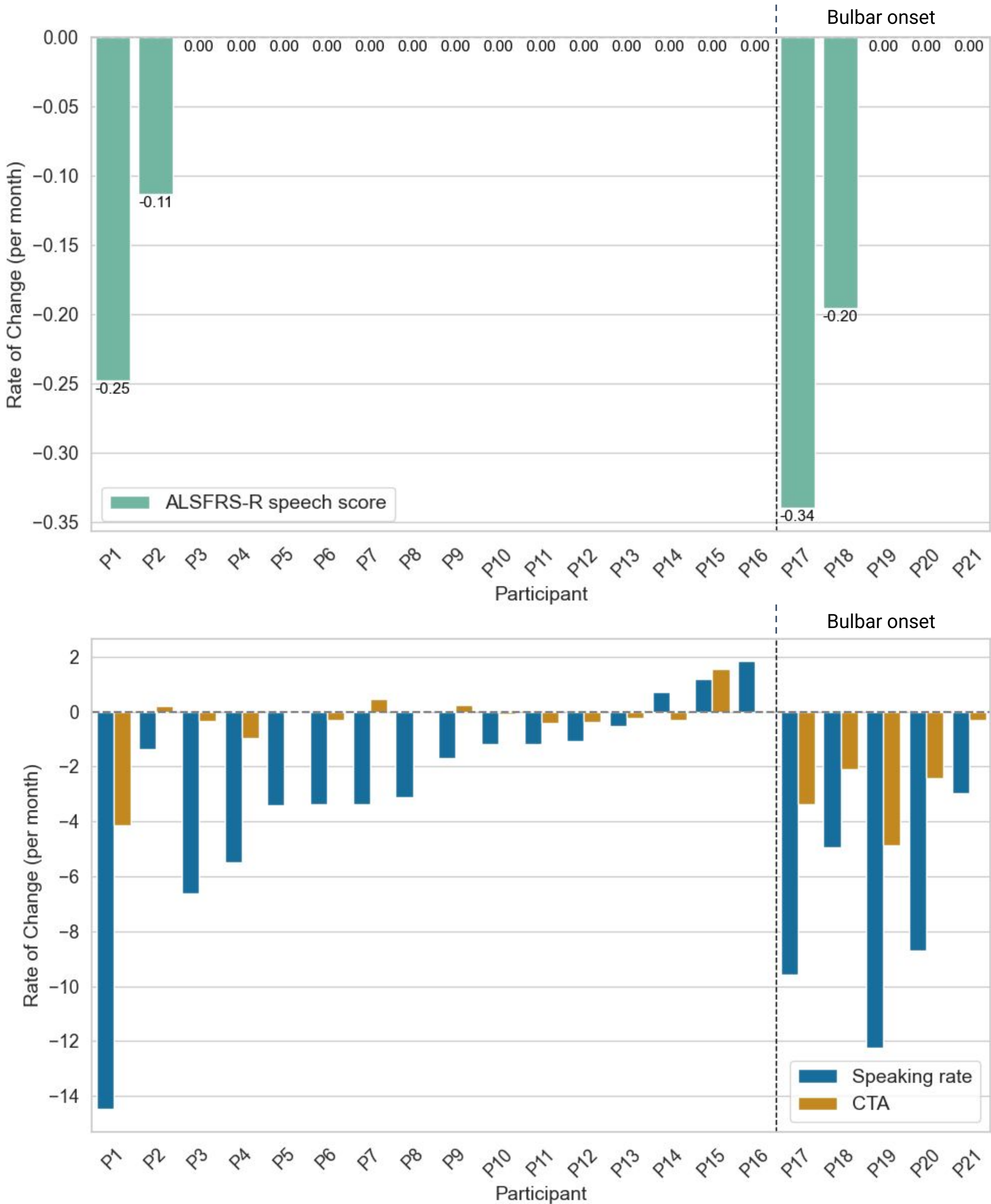


Figure 2. Individual rate of change for 21 participants for ALSFRS-R speech score (top) and speaking rate and CTA (bottom).

Conclusions

- Digital speech biomarkers show significant decline at individual participant level even if the ALSFRS-R speech score remains unchanged
- Speaking rate is a sensitive measure to change in ALS disease progression (in line with existing literature)
- Accounting for learning effect can be important for the interpretation of observations (depending on the type of assessment)
- The present study provides insights on an individual level for a carefully selected cohort matching typical clinical trial criteria