Relationship between sample size and responsiveness of speech-based digital biomarkers in ALS

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Methodological Issue Being Addressed A critical step in designing clinical trial protocols is determining the optimal sample size. The sample size must be small enough to fit budgetary constraints while at the same time an underpowered trial may result in a statistically inconclusive outcome, thus deeming the trial a failure. The estimated costs of measuring the benefits of new therapeutic agents rise exponentially as more patients and clinic visits are required to establish a drug effect. Smaller patient sample sizes are especially desirable in clinical trials for ALS, a rare neurodegenerative disorder with an estimated global prevalence of 4.42 per 100,000 people.

Introduction Previous work has highlighted the utility of speech-based digital biomarkers in tracking longitudinal progression of people with Amyotrophic Lateral Sclerosis (pALS) remotely, i.e. without clinic visits. In this study, we investigate how the responsiveness of remote speech-based digital biomarkers varies with respect to patient sample size.

Methods Participants were recruited by EverythingALS and the Peter Cohen Foundation. Data was collected from 129 pALS (64 female; Bulbar onset: n = 35, Non-Bulbar onset: n = 94) between 2020-11-03 and 2023-10-02. Sample sizes of 30, 25, 20, 15 and 10 participants were randomly sampled 100 times from both cohorts, bulbar and non-bulbar. This study specifically evaluates the responsiveness of two timing and intelligibility related speech metrics calculated from read speech (Bamboo passage): percent pause time and canonical timing alignment. We used growth curve models to estimate the trajectory of these two metrics over time with random slopes and intercepts for each participant. Responsiveness was evaluated as: (i) the time taken in weeks to detect deterioration in these measures that is greater than the standard error of the mean value for the cohort (statistical utility) and (ii) the time taken in weeks to detect deterioration greater than the minimal clinically-important difference (clinical utility) anchored to the ALS Functional Rating Scale - Revised (ALSFRS-R) scale.

Results Mean responsiveness of the two digital biomarkers remains stable even with sample sizes as low as 15 per cohort. However, the uncertainty about the mean responsiveness estimate (confidence interval) increases as sample size decreases. Canonical timing alignment is especially responsive with clinically-important changes detected within 3.32 (± 0.05) to 3.78 (± 0.28) weeks when the sample size under consideration decreases from 30 to 10 in the bulbar cohort and within 6.66 (± 0.18) to 7.24 (± 0.43) weeks in the non-bulbar cohort.

Conclusion We find that speech-based digital biomarkers show considerable promise in enabling clinical trial designs with very small sample sizes. The relationship between sample size and mean responsiveness of speech-based digital biomarkers in ALS is somewhat stable when sample sizes range between 10 and 30 participants per cohort. However, the uncertainty about the responsiveness estimate increases as the sample size reduces, which must be factored into the clinical trial design.

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Keywords

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Guidelines I have read and understand the Poster Guidelines

Disclosures Authors HK, MN and VR were salaried employees of Modality.AI, Inc. when this study was conducted and also hold stock options in the company.

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