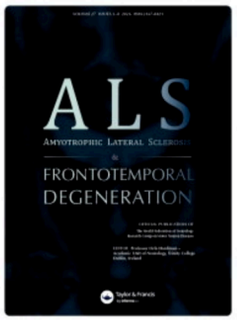

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

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**RESEARCH ARTICLE**

# Minimum important slowing of disease progression as determined by the ALS functional rating scale – a survey of patient expectations toward disease-modifying drugs in ALS

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**Abstract**

*Objective:* To define the minimum important slowing (MIS) of ALS progression that patients would expect from disease-modifying drug treatment in ALS. *Methods:* In a survey of ALS patients, the MIS in ALS progression (change in the ALS Functional Rating Scale–Revised, ALSFRS-R) was assessed by asking: "At what point of slowing of ALS, as determined by the ALSFRS-R, do you consider a drug to be important?" Data were collected during clinic visits or remotely via the ALS App. Participants were differentiated in the prognostic groups of slower (<0.5), intermediate (≥0.5 and ≤1.0), or faster (>1.0) ALS progression (ALSPR; ALSFRS-R/month). *Results:* Of 522 participants (ALS App, $n = 397$; clinic, $n = 125$), 395 (75.7%) completed the survey, while 127 (24.3%) selected the option "cannot estimate". The distribution of MIS was as follows: modest slowing of ALS progression (5% and 10% slowing, $n = 146$ patients, 36.9%), moderate slowing (20%, 30%, and 40% slowing, $n = 135$, 34.2%), and major slowing (≥50% slowing, $n = 114$, 28.9%). Median MIS was 20% (IQR 10–50%). Patients with faster ALSPR more frequently assessed a major slowing as the MIS ($n = 18$, 36.0%) compared to those with slower ALSPR ($n = 54$, 25.2%). *Conclusion:* A considerable number of participants viewed a modest slowing in ALS progression as the MIS, followed closely by preferences for moderate and

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major slowing. Expectations varied according to patients' individual ALS progression. These insights may inform the design of future clinical trials in ALS. Study limitations include potential selection and response biases, as well as the predominantly remote digital assessment.

**Keywords:** *Amyotrophic lateral sclerosis, ALS functional rating scale, ALSFRS-R, minimum important slowing, ALS progression*

## Introduction

Relentless decline in motor function is a hallmark of amyotrophic lateral sclerosis (ALS) (1). The rate of ALS progression, quantified by the monthly change in the ALS Functional Rating Scale–Revised (ALSFRS-R), is widely used to characterize the disease trajectory in both research and clinical practice (2–4). Based on the slope of ALSFRS-R, prognostic groups of ALS progression have been defined and shown to correlate with survival and the biomarker neurofilament light chain (NfL) (5–9). A reduction in the slowing of the functional decline is recognized by regulatory authorities as effectiveness endpoint in ALS drug development programs (10–12). Consequently, most clinical trial protocols have incorporated ALS progression, measured as the change of ALSFRS-R from baseline, as a primary or secondary outcome measure (13,14). Given the pivotal role of ALS progression in the development of ALS treatments, the minimum important slowing (MIS) of ALS progression, which reflects the patient's perspective, is of major interest (15). In a survey among members of the Northeast ALS Consortium (NEALS), ninety per cent of clinical researchers surveyed assessed that a treatment that resulted in a change of 20-25%% or greater in the slowing of the ALSFRS-R would be accepted as "at least somewhat clinically meaningful" (16). More recently, the minimum important difference (MID) for the ALSFRS-R was calculated using standard deviations for participants self-rated as "unchanged" (17). The MID was defined as the absolute difference in mean ALSFRS-R score change between those who reported being "a little worse" and those who reported being "unchanged" or "better". This study yielded an estimated MID for total ALSFRS-R score change of 3.2 over a 6-month timeframe (17). In another study using anchor-based and distribution-based methods, the proposed MID for the ALSFRS-R were 3.8 and 1.2 points, respectively, over a 3-month period (18). However, the patients' perspective toward trial design, and the effectiveness of experimental drugs, remains poorly explored (15). To address this gap, this study explored patients' perceptions of the MIS of ALS progression expected from future disease-modifying treatments in ALS. Specifically, the objectives were i) to investigate the patient′s assessment of MIS of ALS progression, ii) to classify participants into prognostic groups of faster, intermediate, and slower ALS progression, and iii) to compare MIS expectations across these groups.

## Methods

### *Study design*

The investigation was conducted as a prospective, multicenter cohort study from November 2024 until July 2025. The study was reported according to the STROBE criteria (19).

### *Participants*

The participants met the following inclusion criteria: 1) diagnosis of ALS according to the Gold Coast criteria (2,20) consent to data capture using the ALS App (ALS App subcohort); 3) consent to use existing demographic and clinical data.

### *Setting*

**Survey using the ALS app.** Patients were invited to participate in the survey via a mobile application (ALS App), which the includes the self-explanatory version of the ALSFRS-R (ALSFRS-R-SE) as one of its core features (21,22). Non-inferiority of ALSFRS-R assessment via the ALS App compared with data collection during clinic visits has been previously reported (23). The survey on MIS was distributed twice: an initial invitation to participate and one reminder. Independently of the survey and not directly linked to it, participants were monthly invited to complete remote digital assessments of the ALSFRS-R-SE.

**Survey during clinic visit.** Patients were invited to participate in the survey on a printed document, which was handed over to the patient before a regular clinic visit. The survey was completed by the participants without assistance from a healthcare professional. Independently, and as part of standard care, the ALSFRS-R assessment was performed after completion of the MIS survey.

**Contextualization of ALS progression.** Survey participants were informed about their individual ALSFRS-R total score and their individual ALS progression. In the clinic-based cohort, this information was communicated as part of standard clinical care, every 3 to 4 months. Patients of the ALS App cohort, upon monthly completion of the ALSFRS-R-SE assessment, participants received an automated summary, including the ALSFRS-R-SE total score and the calculated progression.

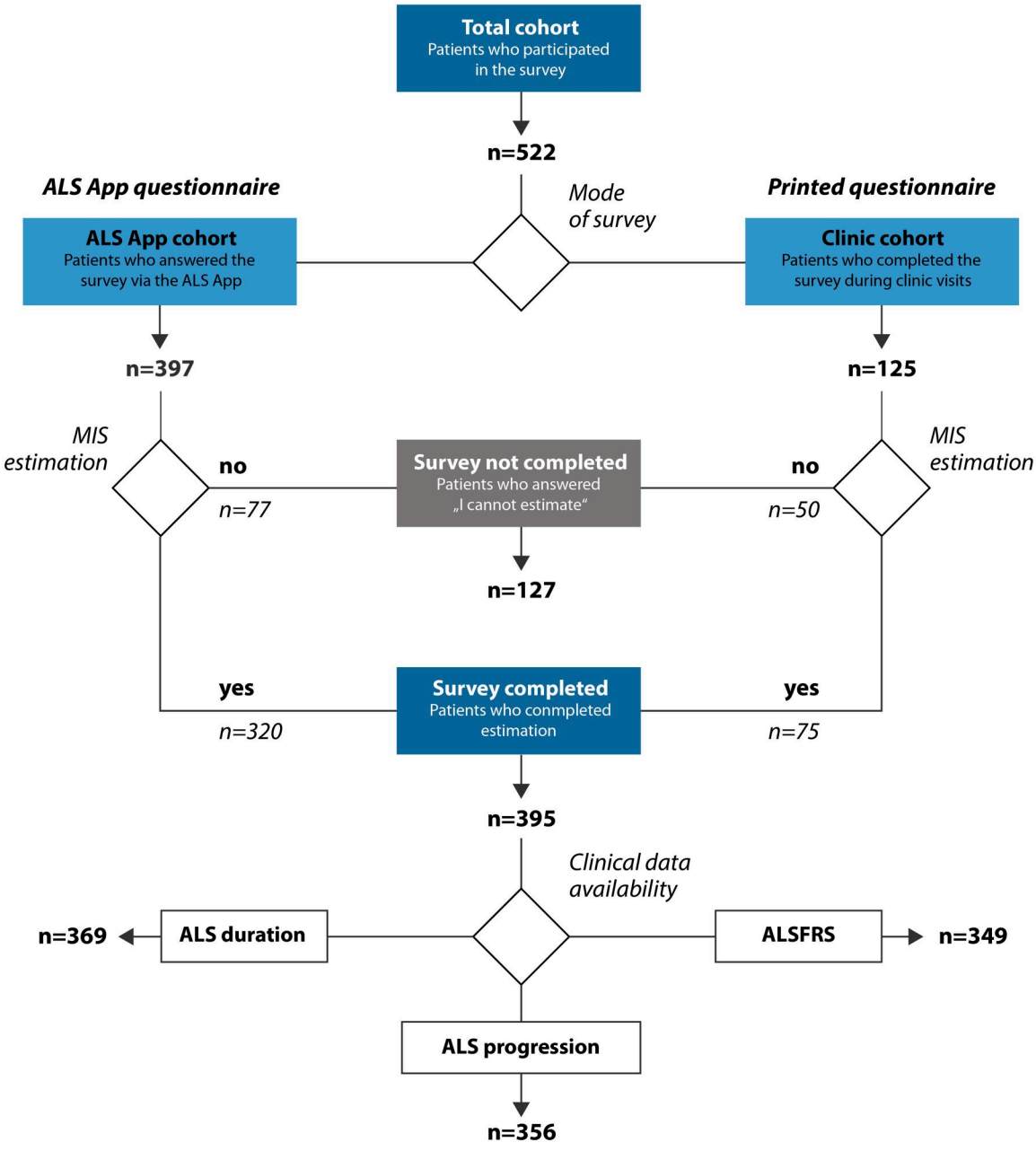


Figure 1. Studied cohort. ALS patients (total survey cohort) were invited to participate in a survey on the minimum important slowing (MIS) of ALS progression. Participants completed the survey either during a clinic visit using a printed questionnaire or remotely via the ALS App. Patients who answered "I cannot estimate" did not complete the survey and were excluded from the analysis. Abbreviations: *n:* number of patients; MIS: minimum important slowing of ALS progression; ALSFRS-R: ALS Functional Rating Scale–Revised; ALS progression: monthly change in ALSFRS-R.

*Description of cohorts*

The total study cohort was comprised of all patients who completed the survey (Figure 1). Patients who answered "I cannot estimate" were excluded from the MIS analysis. The "in-clinic survey cohort" included patients with completed the survey during clinic visits. The "App survey cohort" encompassed participants who answered the survey via the "ALS App" and performed remote digital assessment of ALSFRS-R.

*Protocol approvals and registrations*

The study was approved by the Medical Ethics Committee of Charité – Universitätsmedizin Berlin (EA2/190/23 and EA2/168/20). Written informed consent was obtained from all participants. Patients at any stage of disease were recruited for participation.

*Variables*

**Demographic and clinical characteristics.** Demographic and clinical characteristics were collected (Table 1). ALS duration was calculated based on the number of months between symptom onset and the time of assessment. Disease duration was classified as typical (<5 years), long (≥5 and ≤10 years), and very long ALS duration (>10 years) (8).

Table 1. Demographical and clinical characteristics.

| Characteristics | Description | Total cohort ($n = 522$) | ALS app ($n = 397$) | Clinic ($n = 125$) | $p$-value |
|---|---|---|---|---|---|
| Age (years), $n = 488$ | at onset, mean (SD, R) | 59.3 (10.9; 24.4–86.9) | 58.9 (10.5; 24.4–86.9) | 60.3 (11.9; 29.1–86.6) | 0.235 |
| $n = 522$ | at survey, mean (SD, R) | 63.3 (10.3; 32.8–94.7) | 62.4 (9.8) | 66.1 (11.5; 34.8–94.7) | <0.001 |
| Sex, $n = 522$ | male, % ($n$) | 60.5 (316) | 61.7 (245) | 65.8 (71) | 0.346 |
| | female, % ($n$) | 39.5 (206) | 38.3 (152) | 43.2 (54) | |
| Disease duration (months), $n = 488$ | at survey, mean (SD, R) | 49.7 (51.1; 1.2–336.8) | 42.6 (45.2; 1.2–324.3) | 70.3 (60.7; 8.6–336.8) | <0.001 |
| ALSFRS-R, total, $n = 504$ | first assessment, mean (SD, R) | 38.3 (7.1; 0–48) | 38.8 (6.8; 0–48) | 37.0 (8.0; 0–47) | 0.014 |
| $n = 465$ | at survey, mean (SD, R) | 33.0 (9.5; 0–48) | 34.4 (8.8; 0–48) | 28.8 (10.3; 0–45) | <0.001 |
| ALSPR, total, $n = 474$ | mean (SD, R) | 0.58 (0.64; <0.1–4.3) | 0.61 (0.66; <0.1–4.33) | 0.50 (0.56; 0.04–3.39) | 0.108 |
| ALSPR, classification, $n = 473$ | slower progression, % ($n$) | 60.9 (288) | 57.3 (200) | 71.0 (88) | 0.026 |
| | intermediate progression, % ($n$) | 25.2 (119) | 27.8 (97) | 17.7 (22) | |
| | faster progression, % ($n$) | 14.0 (66) | 14.9 (52) | 11.3 (14) | |

ALSPR: ALS progression; SD: standard deviation; R: range; $n$: number of patients.

**ALSFRS-R and ALSFRS-R-SE.** ALSFRS-R is the main instrument to assess symptoms and motor functions in ALS trials (2,24,25). It comprises 12 items with 5 rating options (0 to 4). The self-explanatory version of the ALSFRS-R (ALSFRS-R-SE) includes instructions and explanations for each item, facilitating the assessment for patients (26). The ALSFRS-R-SE was used for remote digital assessment via the ALS App.

**ALS progression (ALSPR) and classification of ALSPR.** ALSPR was measured by the monthly change of ALSFRS-R scale points and calculated using the following formula: (48 minus ALSFRS-R total score divided by disease duration (months)). A classification of ALSPR of slower (<0.5 ALSFRS-R/month), intermediate (≥0.5 and ≤1.0 ALSFRS-R/month), and faster ALSPR (>1.0 ALSFRS-R/month) was applied as previously described (2–5).

**Classification of functional impairment according to the ALSFRS-R total score.** Disease severity was divided by four groups of functional impairment according to ALSFRS-R total score: 48–37 (moderate impairment), 36–25 (substantial impairment), 24–13 (severe), 12–0 (very severe) scale points (23).

**Minimum important slowing (MIS) of ALS progression.** The survey included a question concerning the MIS of ALS progression with categorical response options. The question stated as follows: "*Future ALS drugs aim to slow the progression of ALS. The slowing of ALS is determined by the ALS Functional Rating Scale. At what point of slowing of ALS – as determined by the ALS Functional Rating Scale – do you consider a drug to be important?*" Eight categorical response options were given: "*5% slowing of ALS, 10% slowing of ALS; 20% slowing of ALS; 30% slowing of ALS; 40% slowing of ALS; 50% slowing of ALS, >50% slowing of ALS; I cannot assess*".

**Three-tier classification of MIS of ALS progression.** To analyze patients' perceptions of the MIS of ALS progression, categorical response options were grouped into three predefined categories based on the percentage of slowing in the ALSFRS-R decline rate. The classification was as follows: modest slowing: 5% or 10% slowing in ALS progression; moderate slowing: 20%, 30%, or 40% slowing in progression; major slowing: 50% or greater slowing in progression. This three-tier approach was applied to facilitate interpretation and statistical comparison of patient responses across clinically meaningful categories.

### *Statistical methods*

Descriptive statistics were calculated for all study variables, including frequencies (percentages) for categorical data and mean, median, standard deviation (SD), and range for continuous variables. Statistical significance was set at $p < 0.05$. The median and interquartile range (IQR) of the MIS were calculated from ordinal response categories (5% to 50% slowing). All analyses were performed using SPSS and StatPlus (Version 7.7.11; AnalystSoft Inc., Walnut, CA, USA).

## Results

**Demographic and clinical characteristics.** Data of 522 patients were included. Of these, 206 were female (39.5%) and 316 were male (60.5%). The mean age at onset was 59.3 years (SD: 10.9; R: 24.4–86.9 years) and the mean ALSPR was 0.58 points/month (SD: 0.64; R: <0.01–4.33). Demographic and clinical data are shown in Table 1.

**MIS in total cohort.** When evaluating the MIS of ALS progression with disease-modifying drugs, most participants ($n = 146$; 36.9%) considered a modest slowing (5% or 10%) as the MIS, followed by preferences for moderate slowing (20%, 30%, or 40%; $n = 135$; 34.2%) and major slowing (≥50%; $n = 114$; 28.9%). The median MIS of ALS progression in the total cohort was 20% (IQR 10–50%). A wide spectrum of subjective perception of MIS was found, in which 23.5% of respondents ($n = 93$) assessed a 5% slowing in ALS progression to be important, whereas 14.7% ($n = 58$) stated a slowing of more than 50% to be minimally important. The detailed survey results are shown in Figure 2 and Table 2.

**MIS in correlation to ALSPR.** Among patients with slower ALSPR, representing the largest subgroup, a modest slowing was most frequently considered meaningful (39.7%; $n = 85$). In patients with intermediate ALSPR, a modest and moderate slowing was mostly perceived as beneficial (68.5%, $n = 63$) and a major slowing of progression was more often defined as minimally important (31.5%, $n = 29$). Patients with faster ALSPR more often perceived a major slowing as the MIS ($n = 18$, 36.0%) when comparing with those with slower progression ($n = 54$, 25.2%) (Table 2 and Figure 3).

**MIS in correlation to ALSFRS-R total score.** When disease severity was classified by ALSFRS-R total score, patients with moderate functional impairment (ALSFRS-R-SE 48–37) more frequently indicated a modest or moderate MIS. By contrast, participants with very severe motor impairment (ALSFRS-R ≤ 12) clustered into two main subgroups: those reporting a modest MIS ($n = 7$, 53.8%) and those reporting a major MIS ($n = 4$, 30.8%). Detailed results are provided in Table 2 and illustrated in Figure 4.

**MIS in correlation to ALS duration.** Most patients with typical ALS duration regarded a modest (35.7%) or moderate (35.8%) slowing of ALS progression as the MIS, whereas the MIS of major slowing was less frequently assessed (28.5%). In contrast, participants with very long disease duration were dived in two larger groups of MIS of modest (41.4%) and major (31.0%) slowing. Detailed results are presented in Table 2 and Figure 5.

## Discussion

The ALSFRS-R has been established as the primary endpoint in most clinical trials of investigational drugs in ALS (6,10–12). Accordingly, the slowing of ALS, measured by the change in ALSFRS-R during the treatment interval, serves as the primary trial objective. Previously, the MID of the total ALSFRS-R has been recognized as pivotal for trial design from both the sponsors' and regulators' perspectives (15). MID refers to the smallest observed change in an outcome measure that patients perceive as meaningful and requires longitudinal assessment with anchor-based or distribution-based methods (27). Recently, the estimated MID for the ALSFRS-R was grounded in the patient perspective of disease progression (17,18). Using anchor-based and distribution-based approaches, a MID for the ALSFRS-R over a 3-month period of 3.8 and 2.0 points were proposed. These estimates correspond to MID in the slowing of ALS progression of 1.3 and 0.7 points per month (18). In addition to previous investigations of MID, this study contributes to the understanding of the MIS of the ALS progression as it (i) obtained patients' expectations specifically in the context of investigational drugs; (ii) focused primarily on the slowing of ALSFRS-R, which is closely aligned with the objectives of most ALS trials; (iii) differentiated the patients' expectations according to disease progression and other clinical criteria, and iv) investigated patients in a broad spectrum of ALS progression, disease duration and functional impairment. This study of MIS elicited prospective judgments about hypothetical slowing of ALSFRS-R decline rather than experienced change. As limitation, no baseline-to-follow-up comparison was performed, and no external anchor of perceived change was applied. Consequently, the methodological requirements for MID estimation were not met. The MIS framework therefore represents a distinct, expectation-based construct that captures patients' treatment-relevant thresholds of meaningful slowing and complements existing MID research by addressing a different, patient-centered question relevant to ALS trial design. Accordingly, the reported values should be interpreted as expressions of patient expectations and preferences toward meaningful future slowing of ALS progression, and not as minimally important thresholds in the methodological sense of MID.

**Studied cohort.** This study enrolled an extended number of patients, exceeding the cohorts reported in previous investigations of MID (17,18). This survey on MIS was undertaken either through face-to-face

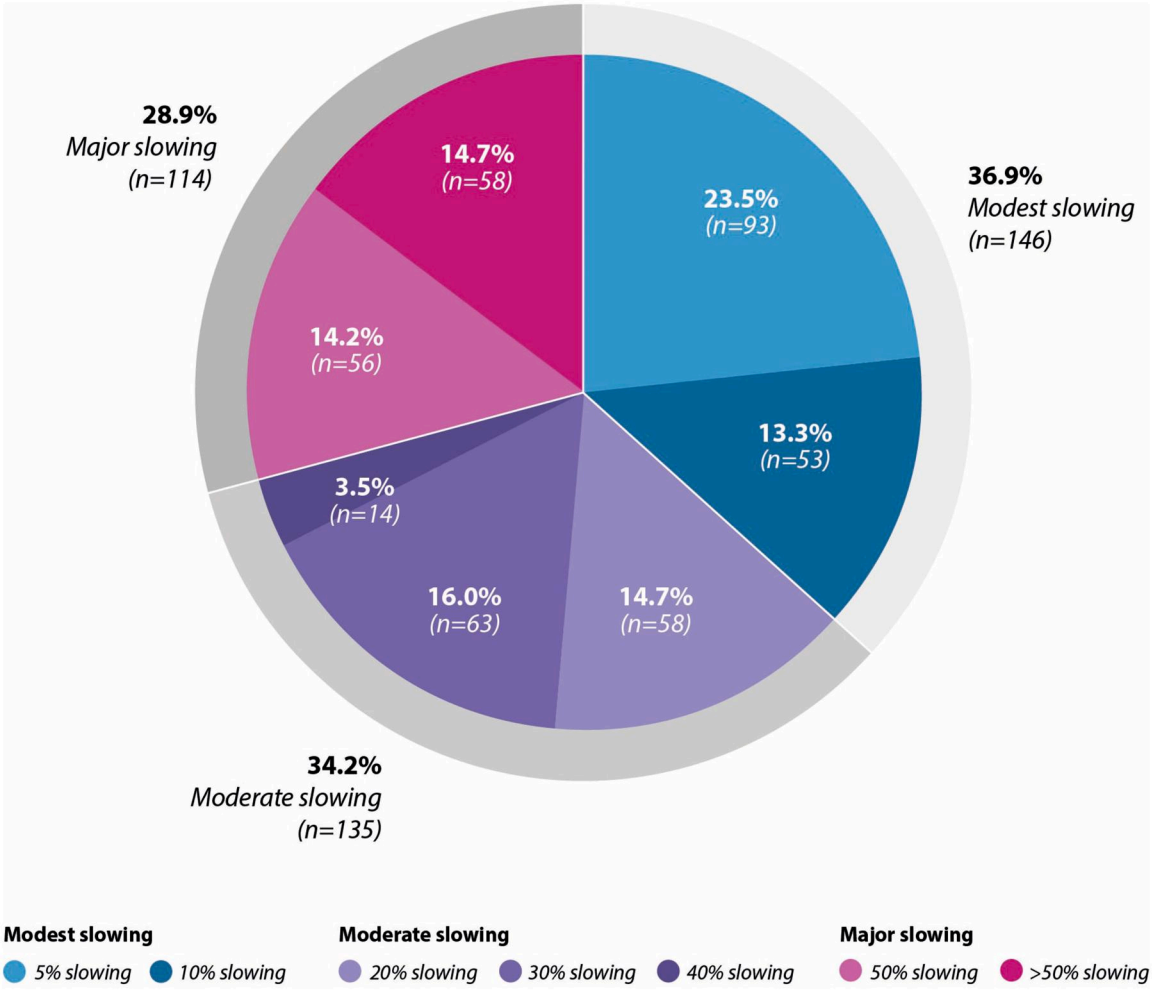


Figure 2. Minimum important slowing of ALS progression. Survey results of a question which stated as follows: *"Future ALS drugs aim to slow the progression of ALS. The slowing of ALS is determined by the ALS Functional Rating Scale. At what point of slowing of ALS – as determined by the ALS Functional Rating Scale – do you consider a drug to be important?"* Eight categorical response options were given: "5% slowing of ALS, 10% slowing of ALS; 20% slowing of ALS; 30% slowing of ALS; 40% slowing of ALS; 50% slowing of ALS, >50% slowing of ALS; I cannot assess". 24.3% ($n = 127$) selected the option "cannot estimate" (not depicted). Three categories based on the percentage of slowing in the ALSFRS-R decline rate were defined: modest slowing: 5% or 10% slowing in ALS progression; moderate slowing: 20%, 30%, or 40% slowing in progression; major slowing: 50% or greater slowing in progression. *n*: number of patients; ALSFRS-R = ALS Functional Rating Scale–Revised.

assessments during clinic visits or remotely via the ALS App (21–23). Digital assessment, applied in 76.1% ($n = 397$) of participants, enabled rapid and efficient enrollment. The advantage of rapid access to patient communities through the ALS App is accompanied with an enrollment bias of younger age, higher ALS progression and shorter disease duration, a bias that has been previously reported (21,23). Importantly, the overall clinical characteristics of participants in this MIS survey were consistent with those reported in other large natural history ALS cohorts (7–9). Of the total cohort, 24% of surveyed patients ($n = 127$) selected the response option "I cannot make an estimation". Remarkably, the proportion of participants who were unable to make an estimation was higher in the clinic cohort (40.0%) than in the ALS App cohort (19.4%). It is conceivable that the patients' prior exposure to the ALSFRS-R may have contributed to differences in response patterns. Given the availability of remote ALSFRS-R assessments in addition to clinic-based assessments, participants in the ALS App cohort may have been more familiar with the scale and the general concept of ALS progression. Alternatively, completing a survey in a home environment may enhance adherence and concentration, resulting in improved response rates. The inability of some participants to provide a MIS estimate may reflect multiple factors, including psychometric limitations of the questionnaire and the inherent complexity of the question. These aspects warrant careful consideration in the design and analysis of future follow-up studies.

**MIS in total cohort.** Reportedly, a survey of ALS experts revealed a minimum clinically important difference (MCID) of 20-25% – from the physician's perspective (16). In this study, the median MIS was 20% (IQR 10–50%) of slowing of ALS progression. These results suggest a general alignment of the physicians' MCID and the MIS from

Table 2. Minimum important slowing of ALS progression.

| Minimum important slowing | 5% % (*n*) | 10% % (*n*) | Modest | 20% % (*n*) | 30% % (*n*) | 40% % (*n*) | Moderate | 50% % (*n*) | >50% % (*n*) | Major | Median % (IQR) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Total (*n* = 395) | 23.5 (93) | 13.4 (53) | 36.9 (146) | 14.7 (58) | 16.0 (63) | 3.5 (14) | 34.2 (135) | 14.2 (56) | 14.7 (58) | 28.9 (114) | 20 (10–50) |
| **Groups of ALS progression (ALSPR)** | | | | | | | | | | | |
| Faster (*n* = 50) | 22.0 (11) | 10.0 (5) | 32.0 (16) | 16.0 (8) | 12.0 (6) | 4.0 (2) | 32.0 (16) | 10.0 (5) | 26.0 13) | 36.0 (18) | 30 (10–>50) |
| Intermediate (*n* = 92) | 20.7 (19) | 13.0 (12) | 33.7 (31) | 13.0 (12) | 19.6 (18) | 2.2 (2) | 34.8 (32) | 14.1 (13) | 17.4 (16) | 31.5 (29) | 30 (10–50) |
| Slower (*n* = 214) | 25.7 (55) | 14.0 (30) | 39.7 (85) | 14.0 (30) | 16.4 (35) | 4.7 (10) | 35.1 (75) | 14.0 (30) | 11.2 (24) | 25.2 (54) | 20 (5–50) |
| **Groups of functional impairment according to ALS functional rating scale (ALSFRS-R)** | | | | | | | | | | | |
| 48–37 (*n* = 150) | 27.3 (41) | 12.0 (18) | 39.3 (59) | 13.4 (20) | 17.3 (26) | 3.3 (5) | 34.0 (51) | 14.0 (21) | 12.7 (19) | 26.7 (40) | 20 (5–50) |
| 36–25 (*n* = 142) | 21.8 (31) | 14.8 (21) | 36.6 (52) | 12.0 (17) | 19.0 (27) | 4.9 (7) | 35.9 (51) | 12.7 (18) | 14.8 (21) | 27.5 (39) | 30 (10–50) |
| 24–13 (*n* = 44) | 22.7 (10) | 6.8 (3) | 29.5 (13) | 27.3 (12) | 9.1 (4) | 2.3 (1) | 38.7 (17) | 13.6 (6) | 18.2 (8) | 31.8 (14) | 20 (10–50) |
| 12–0 (*n* = 13) | 38.4 (5) | 15.4 (2) | 53.8 (7) | 7.7 (1) | 7.7 (1) | 0 (0) | 15.4 (2) | 7.7 (1) | 23.1 (3) | 30.8 (4) | 10 (5–50) |
| **Groups of ALS duration** | | | | | | | | | | | |
| <5 years (*n* = 277) | 22.0 (61) | 13.7 (38) | 35.7 (99) | 14.4 (40) | 18.1 (50) | 3.3 (9) | 35.8 (99) | 13.7 (38) | 14.8 (41) | 28.5 (79) | 20 (10–50) |
| 5 to 10 years (*n* = 63) | 25.4 (16) | 11.1 (7) | 36.5 (23) | 15.9 (10) | 11.1 (7) | 4.8 (3) | 31.8 (20) | 12.7 (8) | 19.0 (12) | 31.7 (20) | 20 (7.5–50) |
| >10 years (*n* = 29) | 27.6 (8) | 13.8 (4) | 41.4 (12) | 10.35 (3) | 10.35 (3) | 6.9 (2) | 27.6 (8) | 20.7 (6) | 10.3 (3) | 31.0 (9) | 20 (5–30) |

SD: standard deviation; R: range; *n*: number of patients.

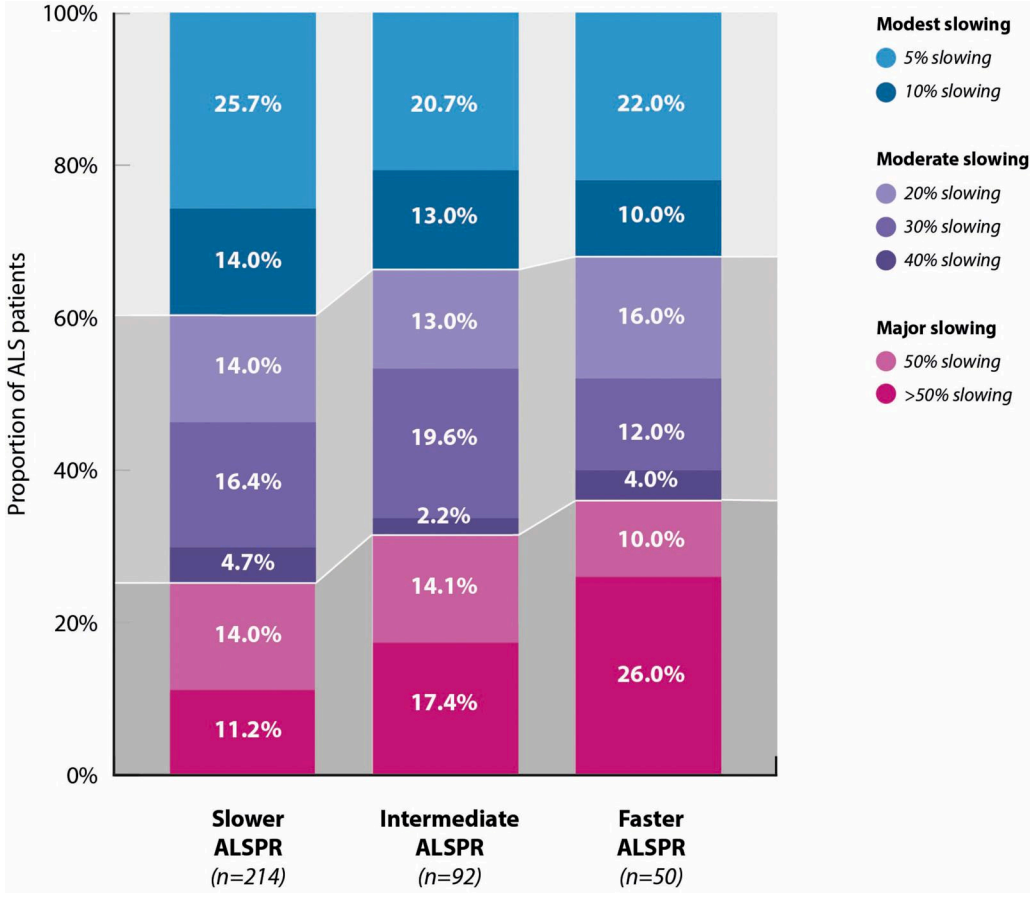


Figure 3. Minimum important slowing of ALS progression in different groups of ALS progression (ALSPR). Participants were grouped for ALSPR as measured by the monthly change of ALSFRS-R scale points. A classification of ALSPR of slower (<0.5 ALSFRS-R/month), intermediate (≥0.5 and ≤1.0 ALSFRS-R/month) and faster ALSPR (>1.0 ALSFRS-R/month) was applied. *n*: number of patients; ALSFRS-R: ALS Functional Rating Scale–Revised.

the and patients′ perspective. Expectedly, a wide spectrum of expectations toward future medicines was found – ranging from 5% to more than 50% of slowing in ALS progression. Overall, 51.7% of participants ($n = 204$) assessed a MIS of 20% or less in the slowing of ALS as beneficial. These findings emphasize the individual perception of MIS, based on clinical characteristics, ALS progression, and other factors that were beyond the scope of this investigation. To reduce the complexity in the presentation of survey results, responses were grouped into categories of modest, moderate, and major slowing of ALS progression. Remarkably, 36.9% of patients considered a modest slowing of disease progression as beneficial, which represents a MIS lower than the expectations reported by clinical experts toward ALS drugs. However, the applied three-tier classification of MIS was based on expert opinion rather than empirical validation.

**MIS in correlation to ALSPR.** The classification of ALSPR into slower, intermediate, and faster trajectories has been established and linked to differences in disease course and survival. Accordingly, the perception of the MIS in the slowing of ALS progression differed between these prognostic groups. Participants with higher ALSPR more frequently regarded a greater degree of slowing as meaningful, whereas individuals with lower ALSPR values more often perceived benefit from smaller reductions in progression. These observations indicate that ALSPR may constitute one of several determinants of the MIS. Notably, a considerable proportion of patients with faster progression considered modest or moderate (64.0%) slowing of ALS to be important. This finding suggests that factors beyond ALSPR, such as personal expectations, value systems, and psychosocial context, contribute to the subjective perception of treatment relevance. The identification of such factors, however, was beyond the scope of the present study.

**MIS in correlation to ALSFRS-R total score.** Given the inclusion criteria of most clinical trials, the group with moderate impairment is the most representative for patients typically enrolled in clinical studies. In this subgroup, a modest MIS of slowing ALS progression predominated (39.3%), followed by expectations of moderate slowing (34.0%). For the design and interpretation of clinical trials, it appears essential to recognize that

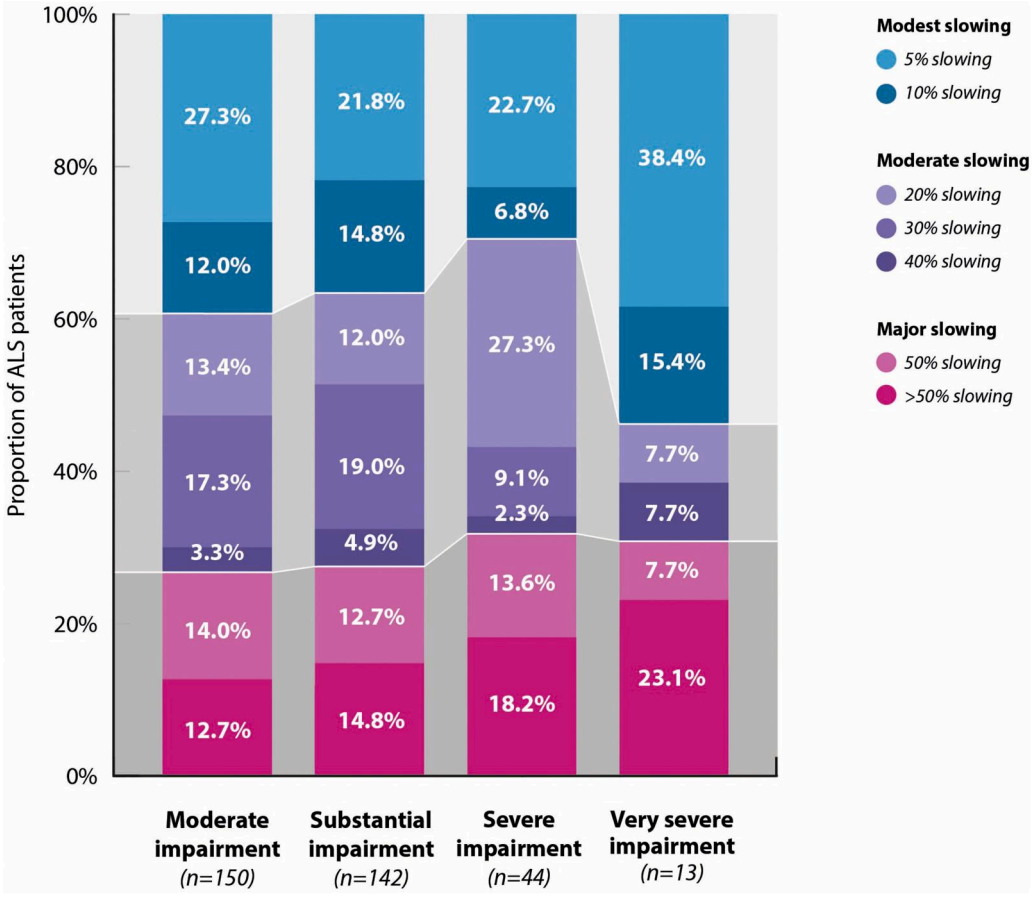


Figure 4. Minimum important slowing of ALS progression in different groups of functional impairment. Survey participants were grouped for functional impairment according to the ALSFRS-R total score: 48–37 (moderate impairment), 36–25 (substantial impairment), 24–13 (severe impairment), 12–0 (very severe impairment) scale points. *n*: number of patients; ALSFRS-R: ALS Functional Rating Scale–Revised.

patients' expectations for meaningful slowing of ALS progression may be lower than the MCID proposed by clinical experts (28,29). A smaller, exploratory subgroup of participants with very severe functional impairment (ALSFRS-R 12–0) clustered into two main response patterns of modest vs major MIS. This finding supports the notion that psychosocial resources, coping strategies, and individual life circumstances – may significantly shape the perception of MIS. However, the small number of participants with very severe functional impairment limits the interpretability of this observation.

**MIS in correlation to ALS duration.** The majority of participants (75.1%) exhibited a typical disease duration (<5 years) in which modest or moderate MIS expectations predominated (71.5%). Conversely, participants with very long disease duration were divided into two main groups, reporting either modest or major MIS values.

## Conclusion

A modest or moderate slowing of ALS progression was considered the MIS for disease-modifying drugs in ALS by half of the survey participants. Notably, patients with differing ALS progression rates, functional impairments, and disease durations exhibited divergent gradations in their perception of what constitutes a meaningful slowing of the disease. The finding that the largest proportion of participants rated modest expectations as sufficient provides valuable insight for the design of future clinical trials. It highlights the need for trial designs capable of detecting small but meaningful effects and for regulators to acknowledge modest slowing of ALS progression as relevant. Several limitations should be considered when interpreting the present findings. Observation and selection biases may have influenced the results due to incomplete response rates and the restriction to patients recruited from specialized centers and through the ALS App. Notably, approximately one quarter of participants were unable to estimate what degree of slowing they would consider important, underscoring the conceptual challenges inherent in expectation-based assessments. Future research should complement MIS by addressing the methodological requirements of MID, including longitudinal study designs with appropriate external anchors. Follow-up studies including a broader clinical spectrum, longer observation periods, and participants from diverse healthcare settings are warranted.

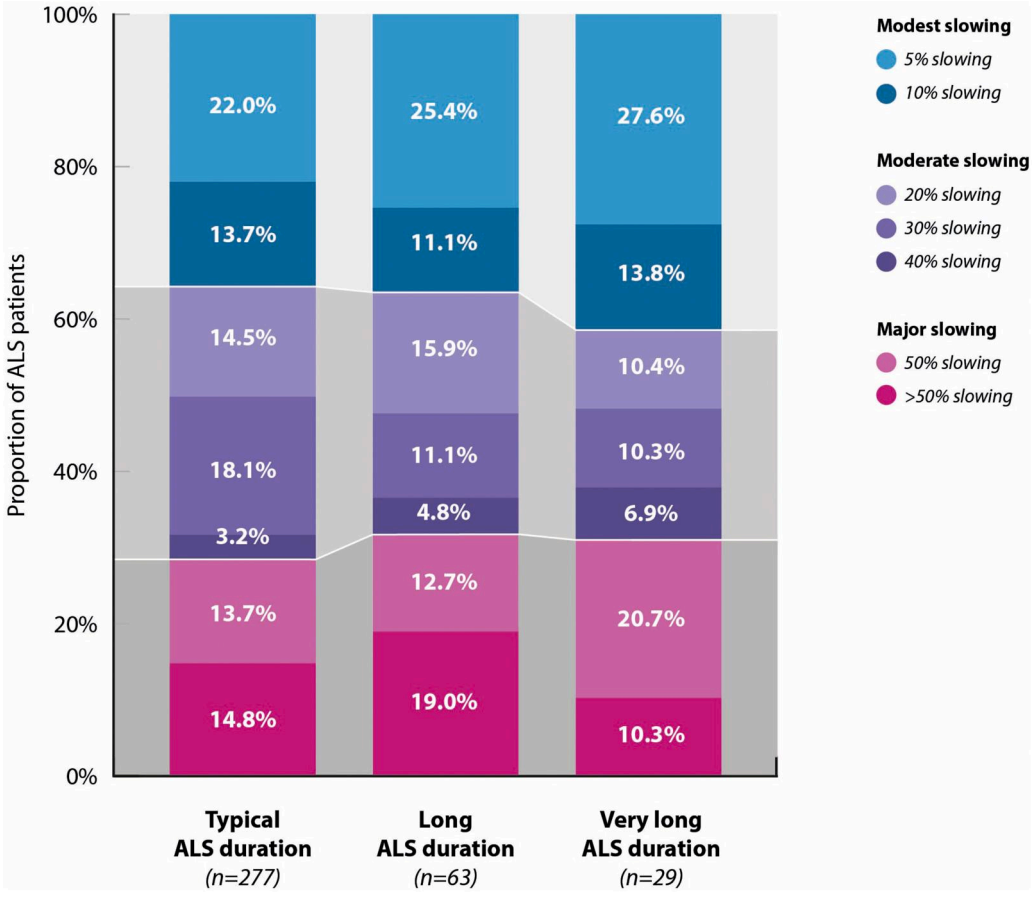


Figure 5. Minimum important slowing of ALS progression in different groups of ALS duration. Survey participants were grouped for typical (<5 years), long (≥5 and ≤10 years), and very long ALS duration (>10 years). *n*=number of patients.

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## Authors contributions

TM, AM and SSP designed and conceptualized the study, analyzed and interpreted the data, and drafted the manuscript for intellectual content. BW, AR, PS, CM, AND SSP had a major role in data collection and preparation of data. TG, UW, AKR, US, RS, JG, BG, SB, PW, FB, SB, RL, BB, MB, PL, DK and JN had a major role in data acquisition and revised the manuscript for intellectual content.

## Declaration of interest

TM has received grants, and research support from AL-S Pharma, QurAlis, Novartis and Prilenia, and served as consultant for Biogen, AbbVie, Voyager Therapeutics, ITF Pharma, Lilly and Trace Neuroscience outside of the submitted work. TM and CM are founders and shareholders of the Ambulanzpartner Soziotechnologie APST GmbH, which makes the mobile application "ALS App". TG has received personal fees from ITF Pharma and served on the advisory boards of ITF Pharma outside of the submitted work. JG has received grants, and research support from AL-S Pharma, QurAlis, and Prilenia, served as consultant for QurAlis, ITF Pharma, and Clene Nanomedicine outside of the submitted work. PW has served on advisory boards of Biogen, ITF Pharma and Novartis outside of the submitted work. SP has received speaker fees, non-financial support and research support from Biogen, Roche, AL-S Pharma, ITF Pharma, and Sanofi and served on advisory boards of Biogen, Roche, Zambon and ITF Pharma outside of the submitted work. PL reports grants from the Bundesministerium für Bildung und Forschung and the Deutsche Forschungsgemeinschaft; consulting fees from AbbVie, Amylyx, Bial, Desitin, ITF Pharma, Novartis, Stadapharm, Raya Therapeutic, Woolsey Pharmaceuticals, and Zambon; and is co-inventor on a patent for the use of fasudil in amyotrophic lateral sclerosis (EP 2825175 B1, US 9.980,972 B2), outside of the scope of the submitted work. The other authors declare no conflicts of interest. AR and SSP are employees of APST, which makes the "ALS App".

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## Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## References

1. Feldman EL, Goutman SA, Petri S, Mazzini L, Savelieff MG, Shaw PJ, et al. Amyotrophic lateral sclerosis. Lancet. 2022;400:1363–80.
2. Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci. 1999;169:13–21.
3. Labra J, Menon P, Byth K, Morrison S, Vucic S. Rate of disease progression: a prognostic biomarker in ALS. J Neurol Neurosurg Psychiatry. 2016;87:628–32.
4. Alves I, Gromicho M, Oliveira Santos M, Pinto S, de Carvalho M. Assessing disease progression in ALS: prognostic subgroups and outliers. Amyotroph Lateral Scler Frontotemporal Degener. 2025;26:58–63.
5. Kimura F, Fujimura C, Ishida S, Nakajima H, Furutama D, Uehara H, et al. Progression rate of ALSFRS-R at time of diagnosis predicts survival time in ALS. Neurology. 2006;66:265–7.
6. Hannaford A, Byth K, Pavey N, Henderson RD, Mathers S, Needham M, et al. Clinical and neurophysiological biomarkers of disease progression in amyotrophic lateral sclerosis. Muscle Nerve. 2023;67:17–24.
7. Caravaca Puchades A, McDonough HE, Al-Chalabi A, Chiò A, Corcia P, Galvin M, et al. Mapping the natural history of amyotrophic lateral sclerosis: time-to-event analysis of clinical milestones in the pan-European, population-based PRECISION-ALS cohort. Amyotroph Lateral Scler Frontotemporal Degener. 2025;26:8–19.
8. Meyer T, Salkic E, Grehl T, Weyen U, Kettemann D, Weydt P, et al. Performance of serum neurofilament light chain in a wide spectrum of clinical courses of amyotrophic lateral sclerosis—a cross-sectional multicenter study. Eur J Neurol. 2023;30:1600–10.
9. Meyer T, Dreger M, Grehl T, Weyen U, Kettemann D, Weydt P, et al. Serum neurofilament light chain in distinct phenotypes of amyotrophic lateral sclerosis: a longitudinal, multicenter study. Eur J Neurol. 2024;31:e16379.
10. Shefner JM, Bedlack R, Andrews JA, Berry JD, Bowser R, Brown R, et al. Amyotrophic lateral sclerosis clinical trials and interpretation of functional end points and fluid biomarkers: a review. JAMA Neurol. 2022;79:1312–8.
11. European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis. 2016. Available at: https://www.ema.europa.eu/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-amyotrophic-lateral-sclerosis_en.pdf. Accessed November 1, 2025.
12. Food Drug Administration Center for Drugs Evaluation Research. Guidance for industry: amyotrophic lateral sclerosis: developing drugs for treatment. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM596718.pdf, 2019. Accessed November 1, 2025.
13. Fournier CN. Considerations for amyotrophic lateral sclerosis (ALS) clinical trial design. Neurotherapeutics. 2022;19:1180–92.
14. Genge A, Cedarbaum JM, Shefner J, Chio A, Al-Chalabi A, Van Damme P, et al. The ALSFRS-R Summit: a global call to action on the use of the ALSFRS-R in ALS clinical trials. Amyotroph Lateral Scler Frontotemporal Degener. 2024;25:382–7.
15. Chiò A, Foucher J, Gwathmey KG, Ingre C. Minimum clinically important difference for drug effectiveness in an area of patient-oriented therapeutic goals in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2025;26:389–98.
16. Castrillo-Viguera C, Grasso DL, Simpson E, Shefner J, Cudkowicz ME. Clinical significance in the change of decline in ALSFRS-R. Amyotroph Lateral Scler. 2010;11:178–80.
17. Fournier CN, James V, Glass JD. Clinically meaningful change: evaluation of the Rasch-built Overall Amyotrophic Lateral Sclerosis Disability Scale (ROADS) and the ALSFRS-R. Amyotroph Lateral Scler Frontotemporal Degener. 2023;24:311–6.
18. Boddy SL, Simpson RM, Walters SJ, Bamford H, Walsh T, McDermott CJ, et al. Estimating the minimum important difference in the ALSFRS-R-instrument in people living with MND. Amyotroph Lateral Scler Frontotemporal Degener. 2025;26:249–58.
19. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370:1453–7.
20. Shefner JM, Al-Chalabi A, Baker MR, Cui L-Y, de Carvalho M, Eisen A, et al. A proposal for new diagnostic criteria for ALS. Clin Neurophysiol. 2020;131:1975–8.
21. Meyer T, Spittel S, Grehl T, Steinbach R, Kettemann D, Petri S, et al. Remote digital assessment of amyotrophic lateral sclerosis functional rating scale—a multicenter observational study. Amyotroph Lateral Scler Frontotemporal Degener. 2023;24:175–84.
22. Maier A, Holm T, Wicks P, Steinfurth L, Linke P, Münch C, et al. Online assessment of ALS functional rating scale compares well to in-clinic evaluation: a prospective trial. Amyotroph Lateral Scler. 2012;13:210–6.
23. Steinfurth L, Grehl T, Weyen U, Kettemann D, Steinbach R, Rödiger A, et al. Self-assessment of amyotrophic lateral sclerosis functional rating scale on the patient's smartphone proves to be non-inferior to clinic data capture. Amyotroph Lateral Scler Frontotemporal Degener. 2025;26:495–506.
24. Bakers JNE, de Jongh AD, Bunte TM, Kendall L, Han SS, Epstein N, et al. Using the ALSFRS-R in multicentre clinical trials for amyotrophic lateral sclerosis: potential limitations in current standard operating procedures. Amyotroph Lateral Scler Frontotemporal Degener. 2022;23:500–7.

25. van Eijk RPA, de Jongh AD, Nikolakopoulos S, McDermott CJ, Eijkemans MJC, Roes KCB, et al. An old friend who has overstayed their welcome: the ALSFRS-R total score as primary endpoint for ALS clinical trials. Amyotroph Lateral Scler Frontotemporal Degener. 2021;22:300–7.
26. Maier A, Boentert M, Reilich P, Witzel S, Petri S, Großkreutz J, et al. ALSFRS-R-SE: an adapted, annotated, and self-explanatory version of the revised amyotrophic lateral sclerosis functional rating scale. Neurol Res Pract. 2022;4:60.
27. Devji T, Carrasco-Labra A, Guyatt G. Mind the methods of determining minimal important differences: three critical issues to consider. Evid Based Ment Health. 2021;24:77–81.
28. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Control Clin Trials. 1989;10:407–15.
29. Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. J Clin Epidemiol. 2008;61:102–9.