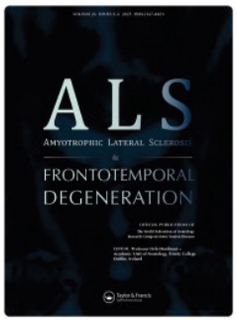

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RESEARCH ARTICLE

Self-assessment of amyotrophic lateral sclerosis functional rating scale on the patient's smartphone proves to be non-inferior to clinic data capture

LAURA STEINFURTH[1], TORSTEN GREHL[2], UTE WEYEN[3], DAGMAR KETTEMANN[1], ROBERT STEINBACH[4], ANNEKATHRIN RÖDIGER[4,5], JULIAN GROSSKREUTZ[6], SUSANNE PETRI[7], MATTHIAS BOENTERT[8], PATRICK WEYDT[9,10], SARAH BERNSEN[9,10], BERTRAM WALTER[1], RENÉ GÜNTHER[11,12], PAUL LINGOR[13,14], JAN CHRISTOPH KOCH[15], PETRA BAUM[16], JOCHEN H. WEISHAUPT[17], JOHANNES DORST[18,19], YASEMIN KOC[1], ISABELL CORDTS[13], MAXIMILIAN VIDOVIC[11], JENNY NORDEN[1], PEGGY SCHUMANN[1,20], PÉTER KÖRTVÉLYESSY[1], SUSANNE SPITTEL[20], CHRISTOPH MÜNCH[1,20], ANDRÉ MAIER[1]* & THOMAS MEYER[1,20]*

[1]*Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt Universität zu Berlin, Berlin, Germany,* [2]*Department of Neurology, Center for ALS and other Motor Neuron Disorders, Alfried Krupp Krankenhaus, Essen, Germany,* [3]*Department of Neurology, Center for ALS and other Motor Neuron Disorders, Berufsgenossenschaftliches Universitätsklinikum Bergmannsheil, Bochum, Germany,* [4]*Department of Neurology, Jena University Hospital, Jena, Germany,* [5]*Jena University Hospital, ZSE, Zentrum für Seltene Erkrankungen, Jena, Germany,* [6]*Department of Neurology, Universitätsmedizin Schleswig-Holstein, Campus Lübeck, Lübeck, Germany,* [7]*Department of Neurology, Hannover Medical School, Hannover, Germany,* [8]*Department of Neurology, Münster University Hospital, Münster, Germany,* [9]*Department for Neurodegenerative Disorders and Gerontopsychiatry, Bonn University, Bonn, Germany,* [10]*DZNE, Deutsches Zentrum für Neurodegenerative Erkrankungen, Research Site Bonn, Bonn, Germany,* [11]*Department of Neurology, Technische Universität Dresden, University Hospital Carl Gustav Carus, Dresden, Germany,* [12]*DZNE, Deutsches Zentrum für Neurodegenerative Erkrankungen, Research Site Dresden, Dresden, Germany,* [13]*Department of Neurology, Technical University of Munich, School of Medicine, Klinikum rechts der Isar, Munich, Germany,* [14]*DZNE, Deutsches Zentrum für Neurodegenerative Erkrankungen, Research Site Munich, Munich, Germany,* [15]*Department of Neurology, Universitätsmedizin Göttingen, Göttingen, Germany,* [16]*Department of Neurology, University Hospital Leipzig, Leipzig, Germany,* [17]*Division for Neurodegenerative Diseases, Neurology Department, University Medicine Mannheim, Heidelberg University, Mannheim Center for Translational Medicine, Mannheim, Germany,* [18]*Department of Neurology, Ulm University, Ulm, Germany,* [19]*DZNE, Deutsches Zentrum für Neurodegenerative Erkrankungen, Research Site Ulm, Ulm, Germany, and* [20]*Ambulanzpartner Soziotechnologie APST GmbH, Berlin, Germany*

Abstract

Objective: To investigate self-assessment of the amyotrophic lateral sclerosis functional rating scale–revised (ALSFRS-R) using the patient's smartphone and to analyze non-inferiority to clinic assessment. *Methods*: In an observational study, ALSFRS-R data being remotely collected on a mobile application (App-ALSFRS-R) were compared to ALSFRS-R captured during clinic visits (clinic-ALSFRS-R). ALS progression rate (ALSPR)—as calculated by the monthly decline of ALSFRS-R—and its intrasubject variability (ALSPR-ISV) between ratings were used to compare both cohorts. To investigate non-inferiority of App-ALSFRS-R data, a non-inferiority margin was determined. *Results*: A total of 691 ALS

Correspondence: Thomas Meyer, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt Universität zu Berlin, Augustenburger Platz 1, Berlin 13353, Germany. E-mail: thomas.meyer@charite.de
*Contributed equally.

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patients using the ALS-App and 1895 patients with clinic assessments were included. Clinical characteristics for the App-ALSFRS-R and clinic-ALSFRS-R cohorts were as follows: Mean age 60.45 (SD 10.43) and 63.69 (SD 11.30) years ($p < 0.001$), disease duration 38.7 (SD 37.68) and 56.75 (SD 54.34) months ($p < 0.001$) and ALSPR 0.72 and 0.59 ($p < 0.001$), respectively. A paired sample analysis of ALSPR-ISV was applicable for 398 patients with clinic as well as app assessments and did not show a significant difference (IQR 0.12 [CI 0.11, 0.14] vs 0.12 [CI 0.11, 0.14], $p = 0.24$; Cohen's $d = 0.06$). CI of IQR for App-ALSFRS-R was below the predefined non-inferiority margin of 0.15 IQR, demonstrating non-inferiority. *Conclusions*: Patients using a mobile application for remote digital self-assessment of the ALSFRS-R revealed younger age, earlier disease course, and faster ALS progression. The finding of non-inferiority of App-ALSFRS-R assessments underscores, that data collection using the ALS-App on the patient's smartphone can serve as additional source of ALSFRS-R in ALS research and clinical practice.

Keywords: *Amyotrophic lateral sclerosis, amyotrophic lateral sclerosis functional rating scale-revised, self-assessment, ALS-App, remote assessment*

Introduction

The ALS Functional Rating Scale in its revised version (ALSFRS-R) is a severity score reflecting the course of ALS (1,2). The 12-item scale is disease-specific and was designed to assess bulbar symptoms, limb and trunk functions, respiratory symptoms, and the need of ALS-related interventions such as percutaneous endoscopic gastrostomy, noninvasive ventilation, or tracheostomy with invasive ventilation (3). The scale was primarily developed as an outcome parameter in clinical trials but evolved to the most widely applied rating scale in both clinical practice and ALS research (4).

The ALSFRS-R is commonly captured during clinic visits. However, clinic consultations can be burdensome for people with ALS, especially with progressing impairment. As the ALSFRS-R does not rely on physical examination, remote assessment via telephone as well as online was proposed (4–6). This aims to reduce the burden of clinic assessment and to complement data gaps between clinic visits (7,8). The feasibility of the ALSFRS-R for self-rating in terms of a patient-reported outcome, paved the way for its remote digital assessment using online platforms and apps (4,9–12). Nowadays self-assessments and online questionnaires are becoming part of standard practice, using adapted versions of the ALSFRS-R. Furthermore, remote self-assessment may increase the efficiency of clinical studies if the rating of ALSFRS-R is moved to digital data capture, which requires less effort from patients with impaired speech and mobility and less resources of health care professionals (13,14). To support the concept of remote digital assessment, in 2022 a German consensus group developed an annotated German and English version of the ALSFRS-R scale that is self-explanatory and unambiguous (ALSFRS-R-SE) (15). By adding brief explanations and comprehensive wording, the ALSFRS-R-SE allows for assessment without specific training.

The ALSFRS-R is not without its limitations. For example, the scale is multidimensional, representing subdomains rather than reflecting disease severity as a total score. Additionally, it exhibits a floor and ceiling effect, poorly representing milder and more severe disability, respectively. Furthermore, it lacks complete coverage of certain functional deficits. Consequently, questions concerning handwriting provide non-informative data about hand function in cases where the dominant hand is not affected (16–18). Despite these issues, the ALSFRS-R serves as a meaningful clinical decision-making criterion in ALS care and as an established outcome parameter in clinical trials. Furthermore, the ALSFRS-R is basis for calculating the ALS progression rate (ALSPR), that puts the total score of the ALSFRS in relation to the disease duration. The ALSPR is recognized as an independent predictor of survival and was correlated with ALS phenotypes and the biomarker neurofilament light chain (19–22). In clinical trials, ALSPR was applied for patient selection, as well as stratification (21–24). Only recently, ALSPR—as assessed in clinic and remotely—was applied to quantify the treatment response to tofersen (25,26).

Given the increasing use of digital platforms and mobile applications, in particular the introduction of the "ALS-App" in Germany, Austria, and Switzerland, remotely captured ALSFRS-R data have become increasingly available. At the same time, there are uncertainties about the extent to which the data collected remotely is comparable with clinic assessments (27). Here, we report the investigation of remote digital assessment of ALSFRS-R by using a mobile application (ALS-App). The aims of the present study were (1) to assign and evaluate demographic and clinical characteristics to the cohorts of clinic and app assessments, (2) to compare the intrasubject variability of ALSPR of clinic and app data, and (3) to investigate if non-inferiority of remote digital assessment using the ALS-App compared to clinic assessment of ALSPR can be proven.

Methods

Study design

The observational study was conducted as a prospective, multicenter cohort study. The investigation was reported according to the STROBE

criteria (28,29). The study was conducted from May 2020 until April 2024.

Participants

The participants met the following inclusion criteria: (1) diagnosis of ALS according to the Gold Coast criteria (28), (2) consent to electronic data capture using the research platform "APST", and (3) capture of at least two assessments of ALSFRS-R.

Setting

App assessment of ALSFRS-R using the ALS-App (App-ALSFRS-R). Patients were offered a remote digital assessment of the ALSFRS-R on a mobile application (ALS-App), which may be used on smartphones or tablet devices and was available for iOS and Android devices (https://www.ambulanzpartner.de/als-app/). The ALSFRS-R used in the ALS-App was changed from the traditional ALSFRS-R to the ALSFRS-R-SE version on 9 May 2022. After obtaining informed consent, patients received an activation link for the digital data capture. For technical support, a telephone service and email contact were provided. All patients were requested to digitally complete the ALSFRS-R at least once a month.

An automated e-mail reminder was sent directly to the participant once a month.

Clinic assessment of ALSFRS-R (clinic-ALSFRS-R). 16 multidisciplinary ALS centers in Germany and Austria participated in this study and provided ALSFRS-R data and clinical data, obtained during the regular visits. The evaluators—who consisted of neurologists, study nurses, and coordinators—carried out the traditional ALSFRS-R assessments and underwent a certification training in ALSFRS-R assessment. These data were de-identified and served as source data for this study (secondary use of existing data for research purposes).

Description of cohorts. All participants who met the inclusion criteria formed the total study cohort. The "clinic-ALS-FRS-R cohort" included patients with ALSFRS-R assessments during clinic visits. The "App-ALSFRS-R cohort" encompassed participants who performed remote digital assessment of ALSFRS-R using the ALS-App. The "combined ALSFRS-R cohort" included patients who provided at least two assessments in both settings, i.e. clinic and app assessment, at any time during the observation period (Figure 1).

Protocol approvals and registrations. The study protocol was approved by the Medical Ethics Committee of Charité – Universitätsmedizin Berlin, Germany under number EA1/219/15. A signed patient information and informed consent form was obtained from all the participating patients.

Variables

Demographic and clinical characteristics. The following demographic and clinical characteristics were collected: age, sex, and onset of symptoms,

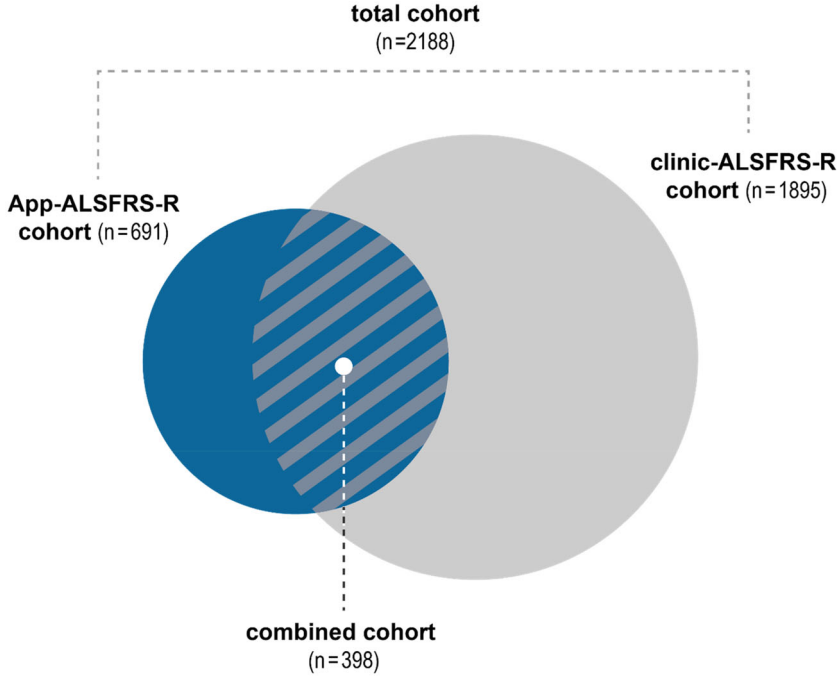

Figure 1. Overview of studied cohorts: remote digital assessment of the ALSFRS-R using the "ALS App" (App-ALSFRS-R) and the assessment during clinic visits (clinic-ALSFRS-R) were investigated. A sub-cohort performed both, ALSFRS-R assessment during clinic visits and remote rating via the "ALS App" (combined cohort). n: number of patients; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale revised.

which was defined as the date (in month and year) of the onset of motor functional deficits: dysarthria, dysphagia, paresis or spasticity of the limbs and trunk or respiratory symptoms. Disease duration was calculated based on the number of months between symptom onset and the time of assessment.

ALSFRS-R. ALSFRS-R is a validated instrument to assess motor functions of the bulbar region, the extremities, the trunk including breathing abilities and the requirement for ventilatory support. It comprises 12 items with 5 rating options (0 to 4). The total range of the scale spans 0 (no function) to 48 scale points (full function). The ALSFRS-R was analyzed for all cohorts of this study.

ALSFRS-R-SE. The ALSFRS-R-SE includes instructions and explanations for each item, facilitating the assessment for healthcare professionals and patients (15). In this study, since 9 May 2022 the ALSFRS-R-SE replaced the ALSFRS-R on the ALS-App.

Classification of disease severity according to the ALSFRS-R total score. Disease severity was divided by four groups of disease severity according to ALSFRS-R total score: 48-37, 36-25, 24-13, 12-0 scale points. The classification was nominally divided from maximum to minimum number of scale points. Based on clinical considerations, this data presentation aimed to group patients from early to advanced stages of motor function deficits as measured by the total ALSFRS-R.

ALS progression rate (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)).

Classification of ALSPR. A classification of ALSPR of slower progressing ALS ($<$0.5 ALSFRS-R/month), intermediate progressing ALS ($\geq$0.5 and $\leq$1.0 ALSFRS-R/month), and faster progressing ALS ($>$ 1.0 ALSFRS-R/month) was applied as previously described (19,20,25,26,30).

Intrasubject variability (ISV) of ALSPR. ISV was assessed as variation of ALSPR: each patient with n ALSFRS-R assessments delivered n approximate ALSPR. To estimate the degree of variation, standard deviation (SD) or interquartile range (IQR) were considered. IQR was more robust against outliers and therefore chosen as the main comparative value.

Statistical methods

Descriptive statistics were used for the statistical analysis (mean, standard deviation in ± and ranges).

Comparison of ISV of ALSPR. Null-hypothesis tests were applied to compare ISV of ALSPR for the App-ALSFRS-R and Clinic-ALSFRS-R cohorts, and to investigate whether or not significant differences could be found. For the total cohort, a linear mixed model was applied, with log ISV as the response variable, group identification (App-ALSFRS-R vs. Clinic-ALSFRS-R) as a fixed effect, and random intercepts for the subject ids accounting for multiple observations for subjects which are present in both cohorts. Two-sample t-tests for paired samples were applicable to assess differences in ISV for the combined cohort.

Non-inferiority margin (δ). To analyze non-inferiority a non-inferiority margin (δ) was determined. Results $< \delta$ would prove non-inferiority, as higher scores would indicate a higher ISV of ALSPR in App-ALSFRS-R data. Statistical reasoning and clinical consideration lead to defining δ (31). The upper CI of the ISV of clinic-ALSFRS-R was determined to be 0.14 IQR, and according to the established method, δ must be chosen close to this margin. In clinical terms, a relatively high variability of the ALSFRS-R has been previously described and was therefore expected (32). From clinical reasoning we determined, that a change in IQR of 0.15 ALSPR would still be acceptable. Thus, δ was determined as 0.15 IQR.

Cohen's d. Cohen's d—or standardized mean difference—was determined to measure the effect size of the differences in ISV for the combined cohort. It was calculated as follows: The mean difference of IQR (mean IQR of App-ALSFRS-R minus mean IQR of clinic-ALSFRS-R) divided by SD for the statistical population. This allowed a standardized evaluation of the mean difference by relating it to standard deviation. The interpretation of the effect size varies in the literature. A commonly used interpretation is based on benchmarks: trivial effect (0.0-0.19), small effect (d = 0.2), medium effect (d = 0.5), and large effect (d = 0.8) (33).

$$d = \frac{\mu_1 - \mu_2}{\sigma}$$

The data were analyzed using "R" Core Team version 4.4.0 (2024-04-24), R Foundation for Statistical Computing, Vienna, Austria.

Results

Number of patients in cohorts

The total cohort encompassed 2188 ALS patients. The App-ALSFRS-R cohort consisted of 691 participants whereas the clinic-ALSFRS-R cohort included 1895 patients. 398 patients were found in the combined ALSFRS-R cohort (Figure 1).

Table 1. Demographic and clinical characteristics of participants.

Characteristics	Classification	Total cohort, n = 2188	Clinic-ALSFRS-R cohort, n = 1895	App-ALSFRS-R cohort, n = 691	*p*-value
Sex	female, % (n)	41% (896)	41% (770)	40% (274)	0.686
	male, % (n)	59% (1292)	59% (1125)	60% (417)	
Age	at onset, years, mean (SD, R)	59.98 (11.84, 1.32 – 88.31)	60.14 (11.96, 1.32 – 87.34)	58.13 (10.89, 25.32 – 88.31)	<0.001
	at time of first assessment, years, mean (SD, R)	63.30 (11.25, 20.78 – 93.75)	63.69 (11.30, 20.78 – 93.75)	60.45 (10.43, 31.47 – 88.92)	<0.001
	at time of last assessment, years, mean (SD, R)	64.49 (11.18, 23.41 – 94.87)	64.87 (11.24, 23.41 – 94.87)	61.36 (10.34, 33.56 – 89.64)	<0.001
Disease duration	at time of last assessment, months, mean (SD, R)	54.06 (52.21, 3.41 – 560.66)	56.75 (54.34, 3.74 – 560.66)	38.70 (37.68, 3.41–560.66)	<0.001
ALS-PR	mean (SD, R)	0.63 (0.58, 0 – 4.94)	0.59 (0.52, 0 – 4.09)	0.72 (0.67, 0 – 4.94)	<0.001
Slower progressing ALS	(<0.5 ALSFRS-R /month), % (n)	54% (1178)	56% (1059)	49% (337)	
Intermediate progressing ALS	(≥0.5 ≤ 1.0 ALSFRS-R/ month), % (n)	27% (596)	27% (505)	29% (200)	
Faster progressing ALS	(> 1.0 ALSFRS-R/ month), % (n)	19% (414)	17% (331)	22% (154)	

n: number of participants; SD: standard deviation; R: range; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised.

Table 2. Demographic and clinical characteristics of the 398 patients in the combined cohort.

Characteristics	Classification			
Sex	female, % (n)	37 (148)		
	male, % (n)	63 (250)		
Age	at onset, years mean (SD, R)	57.5 (10.76, 25.4–84.5)		
		App-ALSFRS-R	Clinic-ALSFRS-R	*p*-value
	at time of first assessment, years, mean (SD, R)	60.01 (10.33, 32.47–87.38)	59.92 (10.29, 32.47–87.33)	0.90
	at time of last assessment, years, mean (SD, R)	61.13 (10.27, 33.56–87.65)	61.11 (10.18, 33.36–87.66)	0.98
Disease duration	at time of last assessment, months, mean (SD, R)	43.29 (42.53, 5.61–560.66)	43.04 (43.44, 3.74–560.66)	0.93
Disease progression	ALSPR mean (SD, R)	0.59 (0.49, 0–3.23)	0.61 (0.48, 0–2.91)	0.41
Slower progressing ALS	(<0.5 ALSFRS-R/month), % (n)	54% (216)	53% (210)	
intermediate progressing ALS	(≥0.5 ≤ 1.0 ALSFRS-R/ month), % (n)	30% (121)	29% (116)	
Faster progressing ALS	(>1.0 ALSFRS-R/month), % (n)	15% (61)	18% (72)	

n: number of participants; SD: standard deviation; R: range; ALSFRS-R: amyotrophic Lateral Sclerosis Functional Rating Scale Revised; ALSPR: ALS progression rate.

Demographic and clinical characteristics

An overview of the demographic and clinical characteristics of the studied cohort is provided in Tables 1 and 2. The App-ALSFRS-R cohort included more patients with faster progressing ALS compared the clinic-ALSFRS-R cohort (22%, $n = 154$ vs 17%, $n = 331$, respectively). Further differences were found between slower progressing ALS (49%, $n = 337$ vs 56%, $n = 1059$), and intermediate progressing ALS (29%, $n = 200$ vs 27%, $n = 505$) (Figure 2).

Intrasubject variability (ISV) of ALSPR

The comparison of ISV of ALSPR for the total cohort was done by linear mixed model analysis. The IQR of the App-ALSFRS-R was reported at 0.171 (CI: 0.150, 0.191) and of clinic-ALSFRS-R 0.129 (CI: 0.119, 0.140). The difference did show statistical significance ($p < 0.001$) (Table 3).

The combined ALSFRS-R cohort was analyzed separately (Table 3). The mean ISV of ALSPR in the App-ALSFRS-R cohort was 0.12 (IQR, CI: 0.11,0.14), and in the clinic-ALS-FRS-R at 0.12 alike (IQR, CI: 0.11,0.14). A two-sample t-test for paired samples confirmed no significant difference in the IQR of ISV in both cohorts (t-test *p*-value: 0.242). The upper limit of CI of App-ALSFRS-R was below the predefined non-inferiority margin, demonstrating non-inferiority.

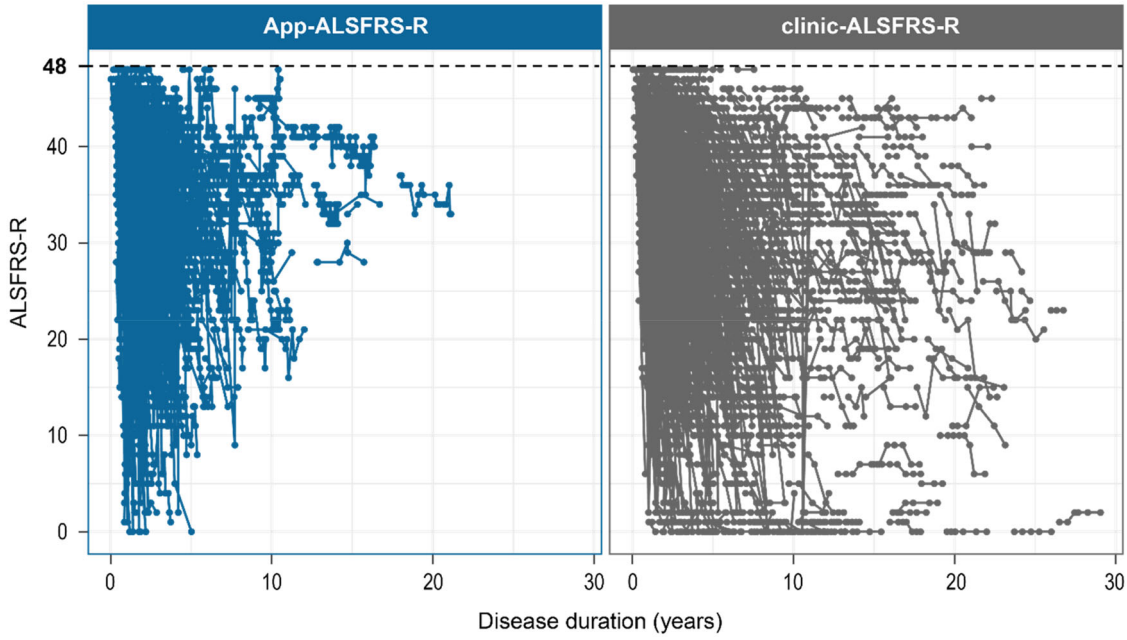

Figure 2. Overview of all App-ALSFRS-R and clinic-ALSFRS-R assessments based on the total score in comparison. Every dot represents one assessment. For depiction purposes, the disease duration was cutoff at 30 years. ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale revised; clinic-ALSFRS-R: ALSFRS-R assessed during clinic visits; App-ALSFRS-R: ALSFRS-R captured via self-assessment on patient's smartphone.

Table 3. Comparison of intrasubject variability (ISV) of ALSPR.

Classification	App mean (95% CI)	Clinic mean (95% CI)	*p*-value
Total cohort			
IQR	0.17 (0.15, 0.91)	0.13 (0.12, 0.14)	<0.001
Combined cohort			
IQR	0.12 (0.11, 0.14)	0.12 (0.11, 0.14)	0.242
Slower progressing ALS (<0.5 ALSFRS-R/month)	0.04 (0.03, 0.04)	0.03 (0.03, 0.04)	0.201
Intermediate progressing ALS (≥0.5 ≤ 1.0 ALSFRS-R/month)	0.10 (0.08, 0.13)	0.10 (0.08, 0.12)	0.733
Faster progressing ALS (> 1.0 ALSFRS-R/month)	0.25 (0.18, 0.33)	0.22 (0.16, 0.29)	0.419

ALSPR: amyotrophic lateral sclerosis progression rate; CI: confidence interval; IQR: interquartile range.

The mean difference in ISV of the ALSPR between App-ALSFRS-R and clinic-ALSFRS-R was 0 (IQR, SD 0.13). To further asses the effect size of this difference Cohen's d was determined. Cohen's d was 0.06 (IQR, CI: −0.14, 0.26), which is interpreted as a trivial effect of the difference in ISV (33) (Figure 3).

ISV of ALSPR in groups of ALSPR

The ISV of three groups of ALSPR of the combined cohort were compared in a subgroup analysis, to assess a possible impact of different ALSPR on ISV. Although statistically not significant ($p = 0.141$), ISV of ALSPR of faster progressing ALS demonstrated a trend toward higher ISV in both, clinic-ALSFRS-R (IQR 0.217, 95% CI: 0.161, 0.292) and App-ALSFRS-R (IQR 0.246, 95% CI: 0.183,0.332; $p = 0.419$) compared to slower progressing ALS with 0.035 (IQR, CI: 0.030, 0.041; $p = 0.201$) and 0.031 (IQR, CI: 0.027, 0.037) as well as intermediate progressing ALS with 0.101 (IQR, CI: 0.080, 0.128) and 0.097 (IQR, CI: 0.077, 0.123; $p = 0.733$), respectively. Significant differences in ISV between clinic-ALSFRS-R and App-ALSFRS-R were not found for any of the studied groups of ALSPR (Figures 4 and 5a).

ISV of ALSPR in groups of disease severity according to ALSFRS-R total score

The comparison between App-ALSFRS-R and clinic-ALSFRS-R did not show significant differences: ALSFRS-R 48-37: 0.051 (IQR, CI 0.043, 0.062) and 0.047 (IQR, CI 0.039, 0.057; $p = 0.362$); ALSFRS-R 36-25: 0.042 (IQR, CI 0.035, 0.051) and 0.037 (IQR, CI 0.031, 0.045; $p = 0.197$); ALSFRS-R 24-13: 0.033 (IQR, CI 0.022, 0.050) and 0.028 (IQR, CI 0.019, 0.043; $p = 0.494$); ALSFRS-R 12-0: 0.053 (IQR, CI 0.015, 0.189) and 0.072 (IQR, CI 0.020, 0.257; $p = 0.651$), respectively (Figure 5b).

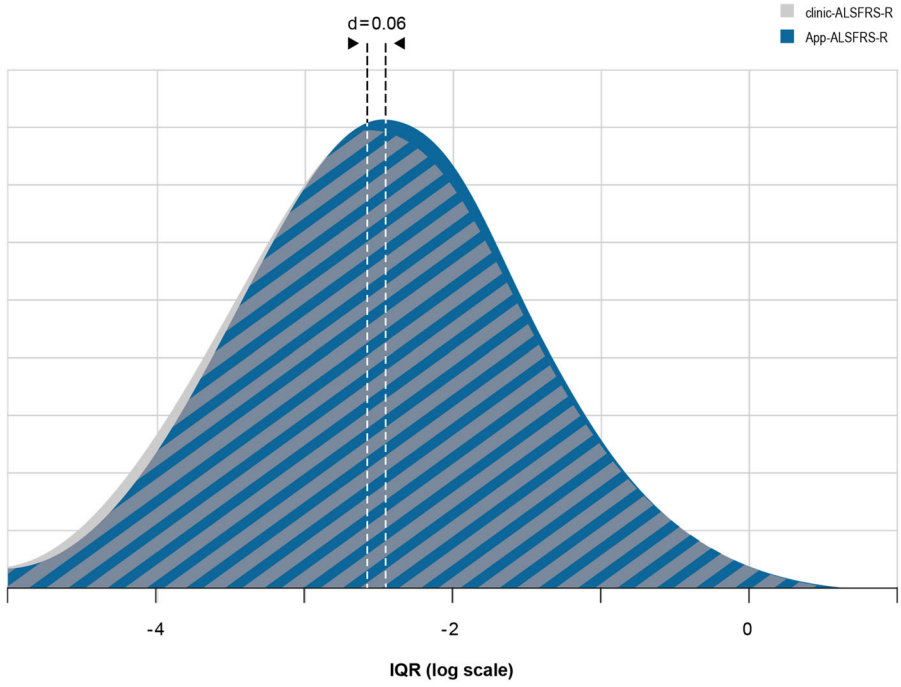

Figure 3. Visualization of Cohen's d. The effect size of the standardized mean difference in intrasubject variability of App-ALSFRS-R and clinic-ALSFRS-R, assessed as interquartile range (IQR), was determined. The result of 0.06 can be interpreted as a trivial effect, meaning the IQR showed an overlap 97.6% for the compared methods. d: Cohen's d; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale revised; clinic-ALSFRS-R: ALSFRS-R assessed during clinic visits; App-ALSFRS-R: ALSFRS-R captured via self-assessment on patient's smartphone.

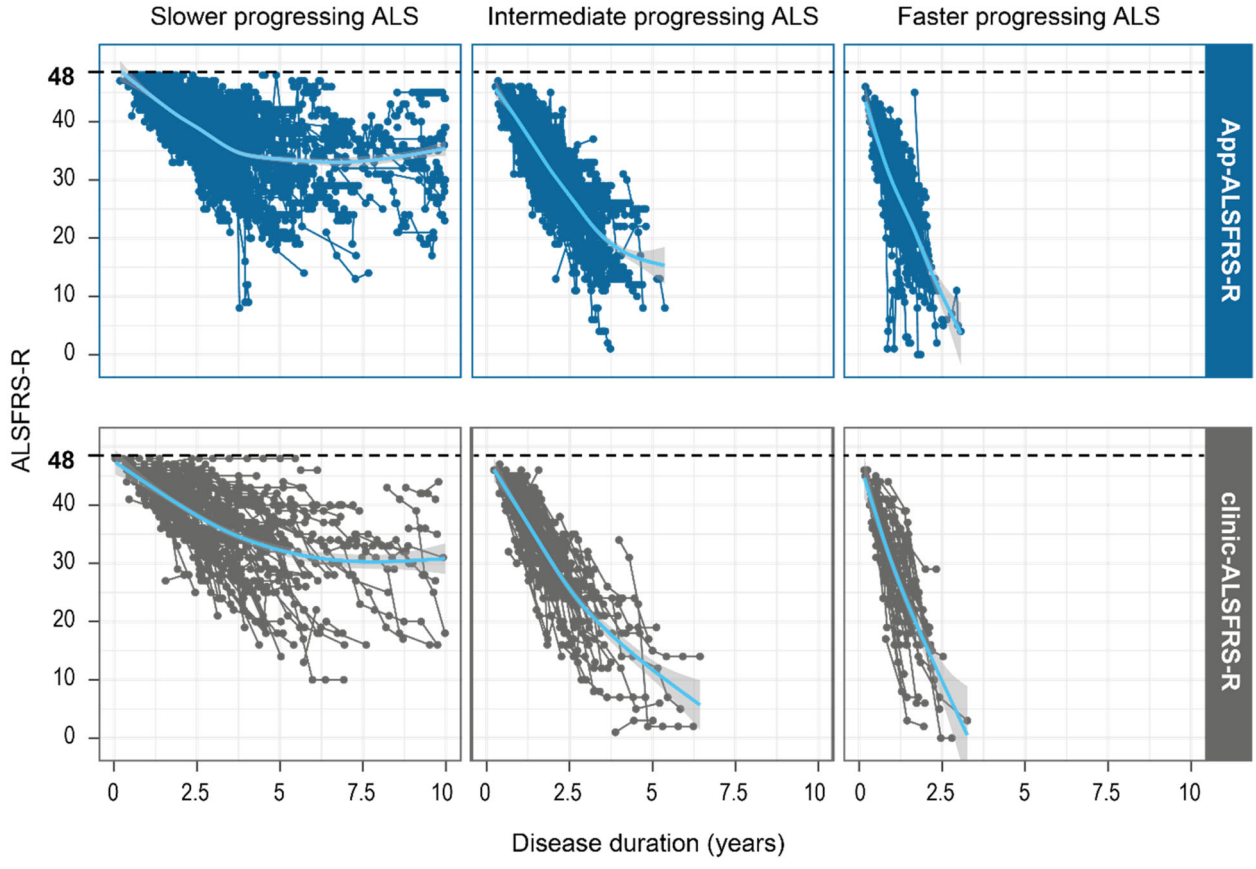

Figure 4. Comparison of clinic and remote assessment of the ALSFRS-R based on the total score. Overview of the assessments of App-ALS-FRS-R and clinic-ALS-FRS-R as analyzed in 3 groups of ALS progression rate (ALSPR), respectively: slower progressing ALS (<0.5 ALSFRS-R/month), intermediate progressing ALS (≥0.5 and ≤1.0 ALSFRS-R/month) and faster progressing ALS (> 1.0 ALSFRS-R/month). Every dot represents one assessment. The mean progression is shown in the blue graph and the shadow represents its variation. ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale revised; clinic-ALSFRS-R: ALSFRS-R assessed during clinic visits; App-ALSFRS-R: ALSFRS-R captured through self-assessment on patient's smartphone.

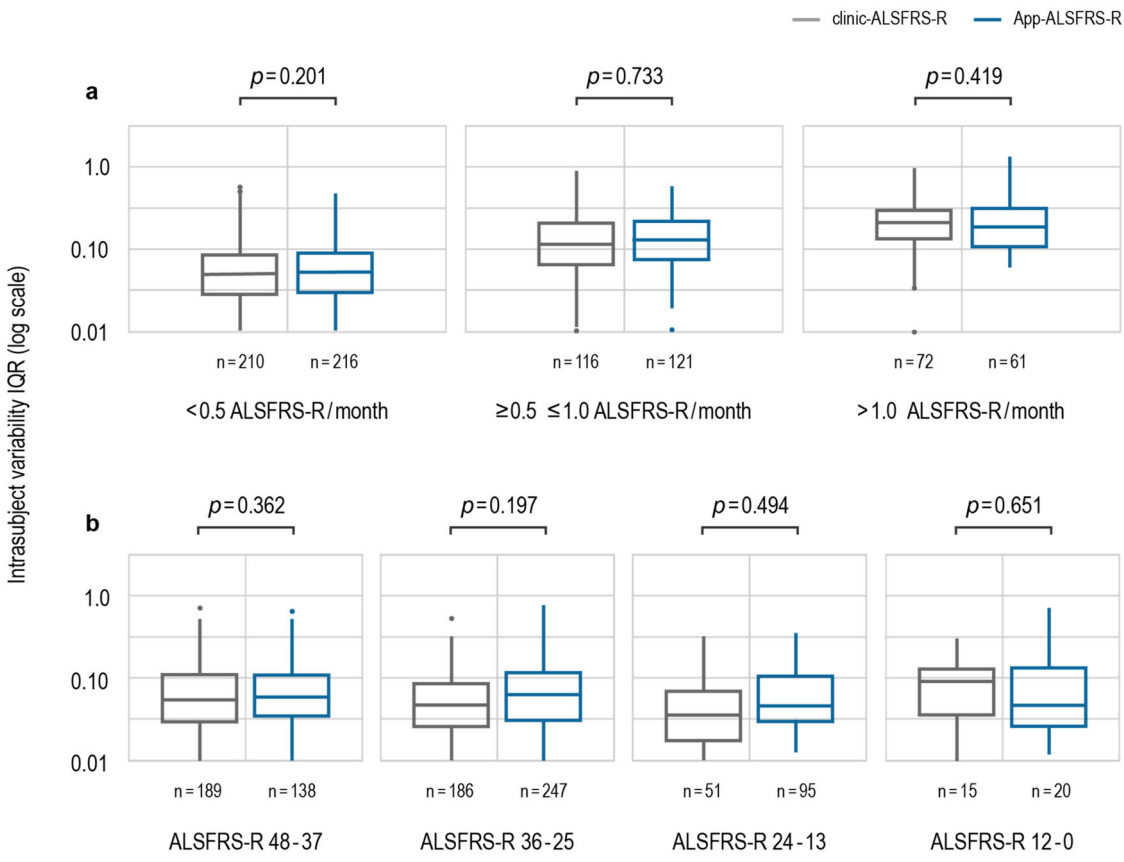

Figure 5. Comparison of clinic and remote assessment of the ALSFRS-R based on the ALS progression rate (ALSPR). The intrasubject variability (ISV) of the ALSPR—as calculated from the ALSFRS-R assessment—was investigated to compare the App-ALSFRS-R and clinic-ALSFRS-R. The analysis was stratified for (a) three groups of ALSPR: slower, intermediate and faster progressing ALS based on the ALSPR and (b) four groups of disease severity according to ALSFRS-R total score. The numbers for each group exceed the total number of patients, as individuals contributed data in several groups of disease severity or ALSPR, respectively. n: number of patients; IQR: Interquartile range; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale revised; clinic-ALSFRS-R: ALSFRS-R assessed during clinic visits; App-ALSFRS-R: ALSFRS-R captured via self-assessment on patient's smartphone.

Discussion

The technological and methodological means for remote digital assessment of ALSFRS-R is on the rise for several years (7). This trend has been supported by previous reports on a strong correlation of on-site and online assessments (6,32,33). This study focussed specifically on ALSFRS-R data capture on the patient's smartphones and the open research question of its non-inferiority when compared to clinic assessment.

Patients' readiness to perform remote assessment of ALSFRS-R was shown before (7) and confirmed in this study. The large number of 691 ALS patients using the ALS-App, who completed at least two assessments of the ALSFRS-R, contribute to the strength of this study. Remarkably, 293 patients remotely provided App-ALSFRS-R data, although they had only realized one clinic visit. Also, the large number of App-ALSFRS-R were generated—in addition to the conventional source of ALSFRS-R data. Both findings contribute to the notion, that digital assessments increase the data density between visits, can potentially fill data gaps of missing visits, or might extend information on the disease course, even when clinic visits are not possible anymore.

Previous studies consistently reported a higher ALSFRS-R total score in digital assessments when compared to clinic-ALSFRS-R data capture (13,34–36). Although this study did not explicitly analyze the differences in total scores, there is a trend suggesting a higher total score for the App-ALSFRS-R. However, this conclusion can only be extrapolated from the higher overall ALSPR and higher proportion of faster progressing ALS for the clinic-ALSFRS-R cohort as observed in the combined cohort (Table 2). In line with previous research on digital assessment of the ALSFRS-R, participants of remote assessment were younger and earlier in the course of ALS (7). This difference may be explained by a selection bias related to technical barriers as well as time efforts of using of digital and telemedicine devices (7,17,35–37). Thus, the ALS-App was commonly offered at the patient's first visit in the respective study centers. Patients with a very long disease course were possibly not considered by the recruiters. Furthermore, it is conceivable that patients in the earlier course of ALS were overrepresented as the

ALS-App may have received more attention in patients with newly diagnosed ALS. Furthermore, the findings might point to barriers for patients with lower motor functional capacities. Future research must aim to apply patient-centred services, technical support, and app design to warrant patient's access to digital assessment in all phases on the disease. It is worth mentioning though, that compared to other epidemiological data on ALS cohorts, the mean disease duration in this cohort was relatively long (38). A disparity in gender distribution that was previously documented and that was found to be disadvantageous to female participation has disappeared (7,13).

Patients using the ALS-App showed a more aggressive disease progression, as the mean ALSPR was higher, than in the clinic cohort. Correspondingly, faster progressing ALS was overrepresented in the ALS-App cohort. This finding suggests that self-assessment of ALSFRS-R on a mobile device is feasible for patients even with faster progressing ALS and of importance when considering remote digital assessments in clinical trial settings. Also, in clinical practice, as a faster progression can make clinic visits more burdensome or even impossible, this observation supports the feasibility of the App use in a wide clinical spectrum of ALS. The differences between faster and slower progressing ALS among ALS-App users can be discussed from a different angle—patients with a more aggressive disease course might perceive more relevance and need to report on the progression of ALS than patients with a slower disease course. At the same time, patients with slower disease and less changes in the ALSFRS-R over time might be less motivated to frequently and continuously provide self-ratings.

Inter- and intrarater variability of ALSFRS-R and ALSPR was in the focus of this investigation. Previous reports have shown conflicting results for ISV on remote self-report measures. Most studies showed a lower ISV, while one study showed a wider range of variability and called for further improvements in remote self-assessment of the ALSFRS-R (6,13,35,37). The clinic-ALSFRS-R cohort was subject of both, inter- and intrarater variability, as the assessment during clinic visits was performed by variable raters that might have changed from visit to visit. In principle, in the ALS-App cohort only intrarater variability was assumed. However, it cannot certainly be excluded that some patients shared login data and authorized relatives to perform the assessment. In this unwanted constellation interrater variability was caused, which belongs to the limitations of the study.

The comparison between the clinic and app cohort as well as the investigation of non-inferiority was performed based on ALSPR, but not ALSFRS-R total score. When predicting the course of ALS in clinical practice and trials, ALSPR, commonly named "slope" or "delta ALSFRS-R", is more informative than the total score (23). This study revealed no difference of ISV of ALSPR between App-ALSFRS-R and clinic-ALSFRS-R and CI below a predefined non-inferiority margin for the statistically robust combined cohort. Furthermore, the data indicated a trivial (as assessed by Cohen's d) difference. Overall, this study proved non-inferiority of App-ALSFRS-R compared to clinic-ALSFRS-R. When we stratified the combined cohort for classes of ALSPR we found, that the ISV increased from slower to faster progressing ALSPR. Although this was not significant, a higher variability must be expected, when faster progressing ALSPR is investigated.

This may also explain the lower ALSPR-ISV of the total clinic-ALSFRS-R cohort in comparison to the total App-ALSFRS-R cohort, as the latter was characterized by a higher mean ALSPR. Although reasons for differences in the total cohort can be various: e.g. the methodologically caused dependency on the onset date, the longer disease duration in the total clinic cohort compared to the total app cohort and overall different sample sizes.

An important limitation in the presented method is the dependency of the ALSPR on the onset date which is based on the patient's recollection of the time of the start of dysarthria, dysphagia, limb paresis, or (rarely) hypoventilation. The training of evaluators—and even more importantly of the patients—is crucial to define the onset date in a consented and therefore, harmonized manner.

The possible impact of disease severity, as measured by the total score of ALSFRS-R, was studied in the combined cohort and did not show significant difference in ISV of ALSPR. This observation underscored methodological feasibility of ALS-App use during the complete course of disease, including very progressed phases of ALS. On this basis, patients with progressed ALS and greater barriers for clinic visits can be offered to use the ALS-App for digital assessment of ALSFRS-R, mainly to gain functional information and to support care related decision-making from remote. This conclusion comes with some limitation as a non-significant difference in ISV of ALSPR was found in the group lowest motor function (0–12 points). In this stage of the disease, changes in respiratory items (items 10–12) become most relevant which is known to be subject of greatest variability (27). This emphasizes the need for training of evaluators, when assessing the ALSFRS-R and the potential benefits of self-explanatory ALSFRS-R-SE.

During the study, in the app-ALSFRS-R cohort a change from traditional ALSFRS-R to the ALSFRS-R-SE was made. The use of different

versions of the ALS-app is a potential limitation of this study, as it cannot be excluded that the self-assessment results are affected. Other studies are ongoing that include head-to-head comparisons of different versions of the ALSFRS-R, including the ALSFRS-R-SE. In summary, this observational study supported the concept of remote digital assessment of ALSFRS-R and proved non-inferiority of ALSPR data being captured on the patient's smartphone—compared to the clinic assessments. Our findings suggest that app assessments can increase ALSFRS-R data density between clinic visits, might fill data gaps of missing onsite visits or allow the remote assessment of the ALSFRS-R in progressed phases of ALS, when clinic visits are burdensome and in protracted intervals.

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Authors contributions

TM, LS, and AM designed and conceptualized the study, analyzed and interpreted the data, and drafted the manuscript for intellectual content. BW had a major role in data collection and preparation of data. TG, UW, DK, RS, AR, JG, SP, MB, PW, SB, RG, PL, JCK, PB, JHW, JD, YK, IC, MV, JN, PS, PK, SSP, and CM had a major role in data acquisition and revised the manuscript for intellectual content.

Declaration of interest

TM has received grants, personal fees, non-financial support and research support from AL-S Pharma, Amylyx, Cytokinetics, Ferrer, Mitsubishi Tanabe, Sanofi, Orphazyme, and served on the advisory boards of Amylyx, Biogen, and ITF Pharma 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 Amylyx and ITF Pharma outside of the submitted work. SP has received speaker fees, non-financial support and research support from Biogen, Roche, ALS Pharma, Amylyx, Cytokinetics, Ferrer, ITF Pharma, and Sanofi and served on advisory boards of Amylyx, Biogen, Roche, Zambon and ITF Pharma outside of the submitted work. PW has served on advisory boards of Biogen, ITF Pharma and Novartis outside of the submitted work. RG has received grants, personal fees, non-financial support and research support from Biogen and served on the advisory boards of Biogen, Roche, and ITF Pharma outside of the submitted work. MV received travel expenses and non-financial support from ITF Pharma outside of the submitted work. AM has received personal fees, non-financial support, and research support from ITF Pharma and Zambon outside the submitted work. PK received consulting fees from Biogen. 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.

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ORCID

Laura Steinfurth http://orcid.org/0000-0001-5503-1742
Paul Lingor http://orcid.org/0000-0001-9362-7096
Thomas Meyer http://orcid.org/0000-0002-2736-7350

Data availability statement

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

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