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Patient-reported, health economic and psychosocial outcomes in patients with Friedreich ataxia (PROFA): protocol of an observational study using momentary data assessments via mobile health app

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ABSTRACT

Introduction Friedreich ataxia (FA) is the most common hereditary ataxia in Europe, characterised by progressively worsening movement and speech impairments with a typical onset before the age of 25 years. The symptoms affect the patients' health-related quality of life (HRQoL) and psychosocial health. FA leads to an increasing need for care, associated with an economic burden. Little is known about the impact of FA on daily lives and HRQoL. To fill that gap, we will assess patient-reported, psychosocial and economic outcomes using momentary data assessment via a mobile health application (app).

Methods and analysis The PROFA Study is a prospective observational study. Patients with FA (n=200) will be recruited at six European study centres (Germany, France and Austria). We will interview patients at baseline in the study centre and subsequently assess the patients' health at home via mobile health app. Patients will self-report ataxia severity, HRQoL, speech and hearing disabilities, coping strategies and well-being, health services usage, adverse health events and productivity losses due to informal care on a daily to monthly basis on the app for 6 months. Our study aims to (1) validate measurements of HRQoL and psychosocial health, (2) assess the usability of the mobile health app, and (3) use descriptive and multivariate statistics to analyse patient-reported and economic outcomes and the interaction effects between these outcomes. Insights into the app's usability could be used for future studies using momentary data assessments to measure outcomes of patients with FA.

Ethics and dissemination Ethical approval has been obtained from the Ethics Committee of the University Medicine of Greifswald, (BB096/22a, 26 October 2022) and from all local ethics committees of the participating study sites. Findings of the study will be published in peer-reviewed journals, presented at relevant international/national congresses and disseminated to German and French Patient Advocacy Organizations.

Trial registration number ClinicalTrials.gov Registry (NCT05943002); Pre-results.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A longitudinal, international, multicentric approach, collecting real-time data in rare Friedreich ataxia (FA) disease, increasing the validity of the disease-specific, psychosocial, patient-reported and health economic outcomes and generating further reference data.
⇒ Assessing the acceptability, feasibility and usability of a mobile health application (m-health app) to collect real-time health-related quality of life, economic and psychosocial data from patients with FA.
⇒ The methodologically chosen sequence of the daily to monthly data assessments over time will provide insights into the existence of health fluctuations and patients' everyday life.
⇒ The patient's ability to handle the m-health app will influence the data collection and there is a risk of a missing consideration of notifications for awaiting data assessments or a non-adherence of the data assessment sequence, which can strongly affect the study results.

BACKGROUND AND RATIONALE

Although rare, Friedreich ataxia (FA) is the most common hereditary ataxia disease in Europe, with a prevalence of approximately 2–4 cases per 100 000 people.[1] In almost all cases, FA is caused by a homozygous mutation of the FXN gene, which encodes the mitochondrial protein frataxin.[2 3] The mitochondrial deficit leads to the first symptoms appearing between the ages of 8 and 15 years. Thus, neurodegenerative movement disorder often affects people in early adulthood.[4] Muscle weakness, imbalance, poor coordination, sensory loss and speech problems (dysarthria) characterise the initial clinical picture

of FA. The progressive non-curable FA course[5] leads to an increasingly severe functional disability associated with an increasing need for care and informal support, resulting in wheelchair dependency and a reduced life expectancy.[2]

Despite this diagnosis and symptom treatment that aims to stabilise functional status of patients with FA as long as possible, only a few studies investigate the impact of FA on patients' health-related quality of life (HRQoL) and everyday life. The few existing studies on HRQoL revealed an effect of FA on physical domains of HRQoL such as mobility, self-care and daily activities, reflecting the clinical disease status.[6–10] The studies underline the importance of validating disease-specific measures, for example, the Patient-Reported Outcome Measure of Ataxia (PROM-Ataxia), or commonly used generic measures such as the EQ-5D, to reveal if such measures reliably and validly assess the impact of FA on patients' HRQoL and psychosocial health, crucial for future clinical and health economic research in FA.

Chronic diseases in advanced stages with growing functional disabilities result in higher utilisation of healthcare services and informal care provided by relatives, causing a growing economic burden.[11–13] However, evaluation of health service resource use in FA is rare. Two studies conclude that healthcare utilisation is higher in advanced disease stages in FA, with paid home care being the main cost driver.[14 15] However, longitudinal analyses are lacking, and other aspects, such as the effect of recommended treatments on costs, are unknown.

Additionally, Giunti *et al*[14] revealed that informal caregivers of patients with FA are, in most cases, parents (80%), providing, on average, 7 hours per week of informal care to support patients in their activities of daily living. Approximately one-fourth of informal caregivers are unemployed due to FA. Thus, informal care and caregivers' productivity losses cause further indirect costs.[14] Studies in neurodegenerative diseases, such as amyotrophic lateral sclerosis, Parkinson, Huntington's disease or dementia, report an increasing disease severity and an autonomy loss of the patients as relevant factors for an increasing caregiver burden.[15] Although essential findings from these studies may be transferred to the informal care situation of people with FA, evidence concerning the economic burden of FA is still inconclusive, especially from a societal perspective that includes individuals' and caregivers' productivity losses next to the utilisation of healthcare services.

Patients with FA must cope with characteristics of communication disabilities, varying among patients and along the disease progression.[16] Slurred speech, insufficient expression of needs or emotions and problems communicating with others are prominent signs of FA, also affecting the patient's psychosocial health and everyday life. Hearing impairment can also occur in FA, causing further severe communication problems, especially in noisy environments (auditory neuropathy).[17] There is hardly any evidence on how communication disabilities are associated with the patient's psychosocial health, and measures to detect the psychosocial impact of speech and hearing disabilities are lacking. Thus, further research is urgently needed to develop and validate such measures and, finally, evaluate the psychosocial impact of hearing and speech disabilities on patients' psychosocial health in FA.

Although existing studies revealed the first impression of the complex disease picture of FA, challenges in understanding the interactions and inter-relationships among psychosocial, patient-reported and economic aspects need to be analysed thoroughly. In addition, previous studies were based on small sample sizes, annual assessments and retrospective questionnaires, which are likely affected by recall bias, and unable to capture in-depth insights into patients' everyday life and health fluctuations. As a prerequisite for generating this evidence, momentary data collection, known as the experience sampling method, or daily diary method, is an intensive longitudinal research methodology that assesses patients' data on multiple occasions over time. This data collection method can offer more detailed insights in real time and a more comprehensive understanding of the impact of FA on the patients' and families' everyday life.

To obtain a comprehensive picture of the impact of FA on patients' daily life and the healthcare system, the PROFA Study uses an innovative approach through a patient-centric mobile health application (m-health app) and a momentary data collection on a daily to monthly basis over 6 months to assess patient-reported and psychosocial outcomes as well as the economic impact of FA. The main study objectives are as follows:

Validation part of the study

1. Assessing the acceptability, feasibility and usability of an m-health app, Atom5, to collect real-time HRQoL, economic and psychosocial data from patients with FA.
2. Validation of a new measure of hearing and speech disabilities' impact on patients' psychosocial health (Communication in Ataxia (COMATAX).
3. Validation of the generic EuroQol five Dimensions Questionnaire (EQ-5D-5L) and disease-specific PROM-Ataxia Short Form, assessing the psychometric performance of these HRQoL instruments in FA.

Evaluation part of the study

4. Assessing patients' HRQoL and change of HRQoL (health fluctuations) over time and identifying sociodemographic and clinical factors associated with patients' HRQoL.
5. Determining the healthcare resource utilisation and costs for patients with FA from a societal perspective that includes medical, care and informal care costs, and analysing the associations between costs and demographics, clinical variables and evidence-based treatments.
6. Assessing the psychosocial impact of speech and hearing disabilities and identifying associated environmental and personal factors moderating patients' psychosocial health.
7. Evaluating interaction effects between utilisation patterns of healthcare resource use (evidence-based treatment and care), HRQoL and psychosocial health.

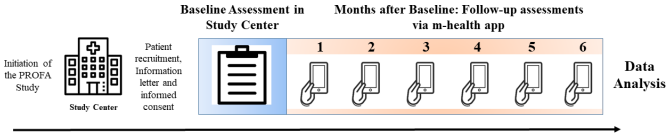

Figure 1 PROFA Study design (simplified). m-health app, mobile health application.

METHODS AND ANALYSIS

Study design

The PROFA Study is a multicentric, prospective, observational study. Eligible patients will be recruited from six study centres in Germany (Aachen, Bonn, Munich and Tübingen), Austria (Innsbruck) and France (Paris), completing a baseline assessment via face-to-face interviews at the six study centres and multiple follow-up remote online momentary data assessments via a m-health app on a daily to monthly basis for 6 months to evaluate the patient-reported, psychosocial and health economic outcomes in FA. The main study design of the PROFA Study is demonstrated in figure 1.

Selection of subjects

Individuals 12 years of age or older with a molecular genetic-confirmed FA diagnosis and an ataxia severity of ≤30 points according to the Scale for the Assessment and Rating of Ataxia (SARA), and with access to a smartphone or a similar digital device will be eligible for study participation. Participants must also be able to consent to the study.

At the six study centres in Germany, France and Austria, participants (or legal representatives) will be verbally informed about the study objectives and procedures by a study centre physician, receive an information sheet and asked to provide informed consent. Participants under the age of 18 years also need the consent of their parents. An overview of the inclusion and exclusion criteria is shown in table 1. The procedure in the study centres is based on the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS).[18]

Table 1 Overview of inclusion and exclusion criteria of the PROFA Study

Inclusion criteria	Exclusion criteria
Genetic diagnosis of FA	Missing FA diagnosis or presence of another ataxia
Ataxia severity SARA score of ≤30 points	Ataxia severity SARA score >30 points
Access to a smartphone or similar digital device	No access to a smartphone or similar digital device
Ability to handle the digital device	Limitations in handling a digital device
Age ≥12 years old	Age <12 years old

FA, Friedreich ataxia; SARA, Scale for the Assessment and Rating of Ataxia.

There are no standard criteria in sample size calculation for this type of study. Thus, the sample size considerations are based on the literature, reporting that more than 90% of validation studies of patient-reported outcome measures include a minimum of 100 participants.[19] In the previous study EFACTS, the same study centres that are also participating in the PROFA Study have recruited n=200 patients with FA. Based on the recruitment of the EFACTS Study, we assume an initial sample size of 200 patients for six study centres within a 1-year time frame. This number was determined based on original prevalence data and the estimated monthly recruitment deemed feasible by the participating European centres.[18]

Patient and public involvement

Two Patient Advocacy Organizations (PAOs) from Germany and France participate in the PROFA Study. The PAOs are involved in (1) the final conceptualisation phase of the study before starting the data assessment to receive added value by confirming the existing and identifying further patient priorities of the PROFA Study and by bringing the patient perspective into the study design; (2) during the study when data assessment is running to evaluate if the study participants are adequately informed about the study and if the assessment procedures are appropriate; (3) after completing the data assessments and analyses to improve the dissemination of the study results using their extensive networks within the FA community and to reach out to policymakers, regulators and other patient organisations. For this purpose, PAOs are members of the executive board of the PROFA Study, attending the annual consortium meetings. This involvement of PAOs will ensure the participation of patients at different levels, the promotion of patients' interests and better dissemination of scientific results into the patient community.

Data assessment procedures

Participants will complete baseline assessments via face-to-face interviews in the Austrian, French and German study centres. Subsequently, participants will self-complete multiple follow-up assessments via a study-specific app (Atom5, Aparito). The app is part of the Atom5 platform that enables remote and digital capture of patient-generated data. Atom5 is ISO 27001 Information Security Management System and ISO 13485 Quality Management Systems accredited and available on both iOS and Google Play stores. It is multilingual and disease agnostic, configured as required for each study protocol. The baseline and follow-up assessments include a broad range of measures, capturing patient-reported and psychosocial outcomes, clinical parameters and healthcare utilisation indicators. Table 2 gives an overview of all instruments and the administration location.

The baseline assessment via interviews at the study centres includes sociodemographics and clinical measures listed in table 2. An individual file will be created for each subject in the Research Electronic Data Capture (REDCap) tool to collect and manage the study centre data. The database will be implemented by the clinician

Table 2 Instruments and sociodemographic variables used in the PROFA Study

Instruments/category	Variables/construct	Administration location
Sociodemographic and medical variables		
	Age, sex, living situation, marital status, education level, employment, family history, FA onset and time of diagnosis, further medical diagnoses, disability stage, drug consumption, medication, general examination	Study centre*
Measures of clinical outcomes		
SARA	Ataxia severity	Study centre*
SARA^{home}	Ataxia severity	Remotely via app†
INAS	Non-ataxia signs/symptoms	Study centre*
FARS-ADL	Subscale for the dimension activity of daily living of the FA Rating Scale	Study centre*
CCAS	Cognitive disability in ataxia	Study centre*
Measures of patient-reported outcomes		
EQ-5D-5L EQ-5D-Y-5L	Health-related quality of life (generic), adult version Health-related quality of life (generic), youth version	Remotely via app† Remotely via app†
PROM-Ataxia Short Form	Health-related quality of life (disease specific)	Remotely via app†
Measures of psychosocial outcomes		
COMATAX	Disabilities in communication	Remotely via app†
Speech records	Rate of speech	Remotely via app†
VHI-30	Subjectively experienced voice disorders	Study centre* and remotely via app†
SSQ-12	Speech perception across multiple domains	Study centre* and remotely via app†
WEMWBS	Psychological well-being	Remotely via app†
Digit triplet test	Early detection of hearing loss	Study centre*
Brief-COPE	Coping strategies for stressful events	Study centre*
Measure of health resource outcomes		
Health utilisation questionnaire based on FIMA and RUD	Utilisation of healthcare services, informal care, caregiver productivity losses, adverse health events	Remotely via app†

*REDCap.
†Atom5 app from Aparito (Wrexham).
app, application; Brief-COPE, Coping Orientation to Problems Experienced; CCAS, Cerebellar Cognitive Affective/Schmahmann Syndrome Scale; COMATAX, Communication in Ataxia; EQ-5D-5L, EuroQol five Dimensions Questionnaire; EQ-5D-Y-5L, EuroQol five Dimensions Questionnaire (youth version); FA, Friedreich ataxia; FARS-ADL, activities of daily living assessment as part of the Friedreich Ataxia Rating Scale; FIMA, German Questionnaire for Health-Related Resource Use; INAS, Inventory of Non-Ataxia Signs; PROM-Ataxia, Patient-Reported Outcome Measure of Ataxia; REDCap, Research Electronic Data Capture; RUD, Resource Utilization in Dementia; SARA, Scale for the Assessment and Rating of Ataxia; SARA^{home}, Scale for the Assessment and Rating of Ataxia at home; SSQ-12, Speech, Spatial and Qualities of Hearing Scale short version; VHI-30, Voice Handicap Index; WEMWBS, Warwick-Edinburgh Mental Well-Being Scale.

in charge or an authorised staff member who has been granted access and modification rights to the database.

After the study centre assessment, patients are given access to the Atom5 Aparito m-health app and downloaded by patients. The study centre clinician will provide a unique QR code for the respective participant to link the participant's mobile device and to set up the home-based momentary data assessment over 6 months. The participants will complete a test survey over the app under the supervision of a clinician.

This is essential to ensure a high-quality data assessment, familiarise the patient with the remote, digital survey and prevent possible handling issues with the app. To improve app usability, a guide for handling the app with information about the completion of tests and surveys, the most common problems and solutions and contact details of the study centre will be handed out to participants. All study centre physicians participating in the study will receive standardised training and a handbook with information about the data collection and

instructions about using the REDCap study centre database and the m-health app assessment.

Subsequently, participants will self-complete tests and surveys daily to monthly for 6 months. The app will send reminders for upcoming assessments and tests, guide the patient through the examinations and surveys, and securely upload the audio-visual data and survey responses.

The sequence of the app-based data collection

The study design includes the following important data assessment aspects. First, we modified the typical frame of a longitudinal study with multiple momentary follow-up assessments at specific time points by implementing monthly data assessments, partly on consecutive days, via the Atom5 app at the patients' homes. This momentary data assessment procedure allows a more reliable assessment of patient outcomes, in-depth information about patients' health state fluctuations within days and the FA impact on patients' everyday life. The administration frequency of each questionnaire is shown in table 3.

The usage of the Atom5 m-health app underlines the current trend of momentary data assessment in research. Various studies have demonstrated the comparability of paper-pencil surveys and electronic data collection across different study populations.[20] Overall, a high acceptance and a preference for electronic devices were seen.[21] The home-based self-rated assessment might

Table 3 Sequence of app-based instruments

Day	SARA^{home}	EQ-5D-(Y)-5L	PROM-Ataxia Short Form	COMATAX	WEMWBS	VHI	SSQ-12	Speech records	Resource Utilization in Dementia
1	✓✓✓	✓✓✓	✓						
8				✓	✓			✓✓✓	
15									
22									
29	✓✓✓			✓				✓✓✓	
36									
43									
50									✓
57	✓✓✓	✓✓✓	✓						
64				✓	✓	✓	✓	✓✓✓	
71									
78									
85	✓✓✓			✓					
92									
99									
106									✓
113	✓✓✓	✓✓✓	✓						
120				✓	✓	✓	✓	✓✓✓	
127									
134									
141	✓✓✓			✓				✓✓✓	
148									
155									
162									✓
169	✓✓✓	✓✓✓	✓						
176				✓	✓	✓	✓	✓✓✓	

✓✓✓: administered on 3 consecutive days.
✓: administered only once.
app, application; COMATAX, Communication in Ataxia; EQ-5D-(Y)-5L, EuroQol five Dimensions Questionnaire (youth version); PROM-Ataxia, Patient-Reported Outcome Measure of Ataxia; SARA^{home}, Scale for the Assessment and Rating of Ataxia at home; SSQ-12, Speech, Spatial and Qualities of Hearing Scale short version; VHI, Voice Handicap Index; WEMWBS, Warwick-Edinburgh Mental Well-Being Scale.

also be a better environment for patients than general study centre visits, where patients have long travels and waiting times, which could cause distress, especially for patients with FA.

Outcome measures

Patient-reported HRQoL

To simultaneously capture wide and disease-relevant HRQoL domains in patients with FA, we will use the generic EQ-5D-5L and the ataxia-specific patient-reported outcome measure PROM-Ataxia Short Form. The EQ-5D-5L is the most widely used utility-based patient-reported outcome measure, covering five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with five levels, ranging from no limitation (level 1) to extreme limitations (level 5).[22] The instrument also has a youth version, the EQ-5D-Y-5L, with the same five dimensions as the EQ-5D-5L but with child-appropriate wording. This youth version will be administered as recommended in the population of ages 12–16 years. The PROM-Ataxia Short Form is an appropriate self-rated measure of ataxia-related symptoms, covering the dimensions of physical and mental health and daily living activities with 10 items.[23] The instrument is the short version of the valid and reliable 70-item PROM-Ataxia questionnaire, developed based on symptom experiences and influenced activities of patients with cerebellar ataxia.[23] Both the EQ-5D-5L and the PROM-Ataxia Short Form are available in German and French but are not validated in patients with FA, representing one objective of the PROFA Study.

Clinical measures

The following clinical parameters will assess the patients' FA status: the SARA,[24] the Inventory of Non-Ataxia Signs (INAS),[25] the activities of daily living assessment as part of the FA Rating Scale (FARS-ADL)[26] and the Cerebellar Cognitive Affective/Schmahmann Syndrome Scale (CCAS).[27 28] All instruments are commonly used in clinical research, are available in a validated German and French form, and will be administered by physicians at the study centres. SARA is also available as an m-health self-application video tool SARA^{home} to assess the severity of ataxia independently at home with remote rating by clinicians[29] and will be, therefore, implemented as a monthly self-examination by patients at their homes via the app. Centralised rating of SARA^{home} videos is conducted by trained investigators according to the specifications of SARA.[24]

Psychosocial impact and speech and hearing difficulties

We will administer the following instruments to assess patients' hearing and communication disabilities: the Voice Handicap Index (VHI-30),[30 31] Speech, Spatial and Qualities of Hearing Scale short version (SSQ-12),[32 33] speech records (repetition on the days of the week during 30s), the digit triplet test (screening auditory test of numbers in adaptative noise),[34 35] psychological well-being (WEMWBS: Warwick-Edinburgh Mental Well-Being Scale)[36 37] and coping strategies of stressful events (Brief-COPE: Coping Orientation to Problems Experienced).[38 39]

To assess self-rated disabilities in communication, the new instrument COMATAX will be developed. To identify basic domains for a new self-questionnaire for the psychosocial impact of hearing and speech disabilities ('COMATAX'), three focus groups with patients with FA, informal and professional caregivers will be conducted. Within these focus groups, participants should directly mention the communication difficulties that affect their psychosocial health. A protocol with open-ended questions related to personal, professional and psychosocial aspects will be used to facilitate the discussion during the focus group meetings. The qualitative analysis of the focus groups will be done by three speech therapists who will independently code the transcriptions of the focus groups for the content analysis until data saturation will be reached. A coding tree will be created by identifying minor themes associated with overall central themes. A bank of items will be elaborated and used to build the new COMATAX scale. Cognitive interviews will be conducted to choose the more precise formulation of items.

Health resource use and costs

Patients' health service utilisation will be assessed by a modified version of the German Questionnaire for Health-Related Resource Use (FIMA).[40] According to the longitudinal study design and the 2-month administration, we reduced the recall period from 3 (in the original FIMA) to 2 months. Informal care and caregiver's productivity losses will be assessed with items of the Resource Utilization in Dementia Lite measure, administering questions about the utilisation of caregiver support for activities of daily living and instrumental activities of daily living and caregivers' short-term and long-term productivity losses.[41] Unlike the original, we will ask patients with FA about the informal caregivers' situation instead of the informal caregivers themselves. Additionally, specific adverse health events will be assessed. These items can be categorised into disease-related, relationship-related and job-related adverse events based on the qualitative study from White *et al*[42] about transitional life events in patients with FA.

Data analysis

The data analysis consists of: (1) an analysis of data based on the validation of the m-health app and of self-reported measures in patients with FA (validation study) and (2) an analysis of factors influencing the daily lives of patients with FA (evaluation study).

Validation of the m-health remote app

We will use descriptive statistics to analyse the app-based assessment's acceptability, feasibility and usability. Thus, information about the usage time and the degree of data completeness of all instruments will be used as relevant indicators. Also, we will integrate a short questionnaire at the end of the app assessment, asking patients to rate the app based on user experience. We hypothesise that a higher ataxia severity—according to video ratings of

SARA^{home} scores—correlates with a higher proportion of missing data. That leads to identifying factors that determine the completeness of data, focusing on age and disease stage as independent factors. Further, we will analyse to which degree low data completeness due to disability can be compensated by the availability of caregivers.

Validation of the COMATAX

The questionnaire will be validated according to acceptability, internal consistency (Cronbach's alpha), discriminative ability (according to SARA scores), convergent validity (according to VHI, SSQ-12, CCAS scores) and test–retest reliability (repeated evaluation with Atom5).

Validation of the EQ-5D-5L and the PROM-Ataxia Short Form

For describing the psychometric performance of the EQ-5D-5L[22] and the PROM-Ataxia Short Form,[23] we will analyse the instruments regarding their distributional properties, reliability, validity, responsiveness and ability to distinguish between groups by sociodemographic (eg, age, gender) and clinically specific components (eg, FA disease stages).

Economic burden: healthcare resource use and costs

Healthcare service utilisation, informal care provision and productivity losses will be monetarised using a standardised unit, opportunity and friction cost approach, respectively, and evaluated from a societal perspective. Costs will be analysed descriptively overall and for each country separately. Multiple linear regression models with non-parametric bootstrapping (skewed cost data) will be used to identify sociodemographic and clinical factors associated with increasing or decreasing costs. Also, we will evaluate the impact of recommended treatments (eg, speech and physiotherapy, early diagnosis) and health events on costs.

HRQoL and health fluctuations

HRQoL and health fluctuation will be assessed with the PROM-Ataxia Short Form[23] and the EQ-5D-5L,[22] using the utility index and the EQ-Visual Analogue Scale. The calculation of the utility index will be based on country-specific value sets. To determine the occurrence, frequency and intensity of the reported health fluctuation, we will make use of the consecutive EQ-5D-5L assessments (3 consecutive days) and analyse the EQ-5D-5L's spread and variability. These findings will be compared with clinically significant differences in the SARA^{home}, using descriptive statistics. We hypothesise that changes in HRQoL over time are influenced by several factors and are not only determined by the clinical characteristics of FA. We will also use generalised estimation equation models with repeated measures to identify factors associated with a higher or lower HRQoL over time.

Hearing and speech disabilities (psychosocial impact)

The COMATAX, VHI[30 31] and SSQ-12 scores[32 33] will be analysed descriptively. Univariate and multivariate analyses will assess associations with neurological evaluation (SARA, INAS, FARS-ADL), the HRQoL (EQ-5D-Y-5L, PROM-Ataxia Short Form), the well-being scale WEMWBS[36 37] and a cognitive evaluation using the CCAS.[27] Acoustic analysis of recorded speech (30s of continued speech 'days of the weeks') and the auditory screening results will be correlated with the self-survey of dysarthria (VHI), hearing loss (SSQ-12) and COMATAX survey. The well-being scores will be compared for each coping/internal strategy profile (Brief-COPE[38 39]) according to the objective and subjective measures of speech and hearing.

Interaction effects between outcomes

Significant interactions between utilisation patterns of health resources, like the utilisation of evidence-based treatment and care, and its costs, patients' HRQoL and the psychosocial impact of communication difficulties, will be analysed using multivariate linear and logistic regression models.

Expected results

The PROFA Study will provide a comprehensive and better understanding of the disease burden of everyday life, determinants of psychosocial health and HRQoL of patients with FA, as well as a detailed description of specific health events, healthcare service utilisation and costs. Based on that, we will be able to describe important sociodemographic and clinical factors, specific treatment patterns, and health events that negatively or positively affect HRQoL and psychosocial health of patients with FA. This knowledge will build the basis for improving the current treatment and living situation in FA. Furthermore, the development of a new measure of the psychosocial impact of hearing and speech disabilities and the validation of existing generic and disease-specific measures of HRQoL will be vital for future research and routine clinical practice. Specifically, our research on speech and hearing and patients' HRQoL will be highly relevant for designing targeted, quality-controlled, standardised treatment and rehabilitation programmes that aim to improve patients' health.

For the first time, the PROFA Study will assess in-depth real-time data in FA by using a remote m-health app. The obtained data on the acceptability and usability of the m-health app can also be used for future studies in FA or other rare diseases using momentary data assessments and interventions that aim to improve outcomes of patients with FA. This underlined the current trend of electronic-based research, reaching now the setting of FA. Patients can state and self-track their health, health service utilisation and specific health events, which could also be beneficial for patients themselves, helping them to monitor and manage all aspects of their health. Additionally, the repeated administration of the outcome measures over the app can better capture important fluctuation of psychosocial health, HRQoL and ataxia severity, probably

drawing conclusions that are more precise from clinical trials in FA.

The novel feature of PROFA concerning clinical outcomes is the combination of conventional clinical assessment with repeated home-based assessments, clinical tests and patient-reported outcomes, providing new insights into the disease's impact on daily life of patients with FA. We will obtain essential and sufficient evidence on the economic burden of FA. Informal care provided by caregivers and the resulting productivity losses of employed caregivers are an important aspect of care and caregiver burden but are currently under-represented in clinical and healthcare research. Thus, this study will provide first insights into country-specific treatment patterns and the informal support for FA.

Overall, the in-depth and multidisciplinary real-time data assessment will provide a better understanding of the FA impact on patients' everyday life, firming the basis for the design of improved care and rehabilitation programmes and future clinical and healthcare research trials. All of this can potentially improve the current treatment, care and living situation of patients with FA and their families.

Ethics and dissemination

The PROFA Study was evaluated and approved by the responsible ethical board (Ethics Committee of the University Medicine of Greifswald, ethical vote number: BB096/22a, 26 October 2022) and from all local ethics committees of the participating study sites (Aachen: Ethics Committee at the RWTH Aachen Faculty of Medicine, ethical vote number 22-014; Bonn: Ethics Committee at the University of Bonn, ethical vote number 440/22; Munich: Ethics Committee of the Medical Faculty, ethical vote number 22-1095; Tübingen: Ethics Committee at the University Tübingen Faculty of Medicine, ethical vote number 672/2022BO2; Innsbruck: Ethics Committee of the Medical University of Innsbruck, ethical vote number 1379/2022; Paris: Comité de Protection des Personnes Est III, ethical vote number: 2023-A00315-40). Furthermore, the study is registered in the ClinicalTrials.gov Register (NCT05943002). All participants and parents of participants under the age of 18 years provide written informed consent. Study participation was only possible with the consent of the parents. The PROFA Study will be conducted according to the Declaration of Helsinki.

Dissemination of the study results will be published in peer-reviewed journals, presented at relevant international/national congresses and disseminated to German and French PAOs.

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Contributors BM, TKloc, MG-E, FX and SBor conceptualised and designed the study. MG-E, KR, TKlop, LS, SBoe and SBor organised the implementation in the respective study centres for recruiting patients and collecting data. MS and AN provided expertise in including the patient perspective in all phases of the study. MB and BM designed and developed the study protocol manuscript. All authors (MB, NW, SBor, SS, FX, JBS, KR, SBoe, TKlop, IK, LS, MG-E, TKloc, EHD, MS, AN and BM) read, revised and approved the final manuscript.

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