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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

Maresa Buchholz[1]*, Niklas Weber[1], Stephanie Borel[2], Sabrina Sayah[2], Feng Xie[3], Jörg Schulz[4,*], Kathrin Reetz[4,5], Sylvia Boesch[6], Thomas Klopstock[7], Ivan Karin[7], Ludger Schöls[8], Marcus Grobe-Einsler[9], Thomas Klockgether[9], Elin Haf Davies[10], Madleine Schmeder[11], Andreas Nadke[12], Bernhard Michalowsky[1]

1. German Center for Neurodegenerative Diseases (DZNE), Site Rostock/ Greifswald, Greifswald, Germany.

2. Sorbonne University, Paris Brain Institute (ICM - Institut du Cerveau), INSERM, CNRS, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France.

3. McMaster University, Department Health Research Methods, Evidence and Impact, Hamilton, Canada.

4. Klinik für Neurologie, RWTH Aachen, Aachen, Germany.

5. JARA Institute Molecular Neuroscience and Neuroimaging, RWTH Aachen & Forschungszentrum Jülich, Aachen, Germany

6. Klinik für Neurologie, Medizinische Universität Innsbruck, Innsbruck, Austria.

7. Friedrich-Baur-Institut an der Neurologischen Klinik und Poliklinik, LMU München, Munich, Germany.

8. Neurologische Klinik und Hertie-Institut für Klinische Hirnforschung, Universitätsklinik Tübingen, Tübingen, Germany.

9. German Center for Neurodegenerative Diseases (DZNE) site Bonn, Bonn, Germany.

10. Aparito Ltd, Wrexam, Wales.

11. Association Française de l'Ataxie de Friedreich, Hirson, France.

12. Deutsche Heredo-Ataxie-Gesellschaft e.V., Stuttgart, Germany.

*** Correspondence:**
Maresa Buchholz, German Center for Neurodegenerative Diseases e.V., Ellernholzstraße 1-2, 17487 Greifswald, Germany, maresa.buchholz@dzne.de

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Abstract

Introduction: Friedreich ataxia (FA) is the most common hereditary ataxia in Europe, characterized by progressively worsening movement and speech impairments with a typical onset before the age of 25. 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 mobile-health app.

Methods and analysis: The PROFA Study is a prospective observational study. FA patients (n=200) will be recruited at six European study centers (Germany, France, and Austria). We will interview patients at baseline in the study center 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 the monthly basis on the app for six months. Our study aims to i) validate measurements of HRQoL and psychosocial health, ii) assess the usability of the mobile-health app, and iii) use descriptive and multivariate statistics to analyze 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 FA patients' outcomes.

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 PAOs.

Trial registration number: Under review **(**Clinical Trials.cov Register).

Strength 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.

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- Assessing the acceptability, feasibility, and usability of a mobile-health (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 for 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.

Keywords: Rare diseases, Friedreich ataxia, patient-reported outcomes, health economics, m-health app assessment, speech and hearing disabilities, health and informal care

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1 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 eight and 15. Thus, neurodegenerative movement disorder often affects people in early adulthood (4). Muscle weakness, imbalance, poor coordination, sensory loss, and speech problems (dysarthria) characterize 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 stabilize FA patients' functional status 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 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 utilization 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 utilization 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, seven hours per week of informal care to support patients in their activities of daily living. Approximately every fourth of informal caregivers is unemployed due to FA. Thus, informal care and caregivers' productivity losses cause further indirect costs (14). Studies in neurodegenerative diseases, such as ALS, Parkinson, Huntington's Disease or dementia, report an increasing disease severity and an

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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 utilization of healthcare services.

FA patients 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 interrelationships among psychosocial, patient-reported and economic aspects need to be analyzed 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 m-health app and a momentary data collection on a daily to monthly basis over six months to assess patient-reported and psychosocial outcomes as well as the economic impact of FA. The main study objectives are as follows:

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Validation part of the study

(1) Assessing the acceptability, feasibility, and usability of an m-health app Atom5™, to collect real-time health-related quality of life, economic, and psychosocial data from patients with FA.

(2) Validation of a new measure of hearing and speech disabilities' impact on patients' psychosocial health (COMATAX).

(3) Validation of the generic 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 utilization and costs for patients with FA from a societal perspective that includes medical, care, and informal care costs and analyzing 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 utilization patterns of healthcare resource use (evidence-based treatment and care), HRQoL, and psychosocial health.

2 METHODS AND ANALYSIS

Study design

The PROFA study is a multi-centric, prospective, observational study. Eligible patients will be recruited from six study centers 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 centers and multiple follow-up remote online momentary data assessment via an m-health app on a daily to monthly basis for six 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.

*** Please insert here Figure 1: PROFA study design (simplified) ***

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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 centers in Germany, France, and Austria, participants (or legal representatives) will be verbally informed about the study objectives and procedures by a study center physician, receive an information sheet, and asked to provide informed consent. Participants under the age of 18 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 centers 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

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 centers that are also participating in the PROFA study have recruited n= 200 FA patients. Based on the recruitment of the EFACTS study we assume an initial sample size of 200 patients for six study centers within a one-year timeframe. This number was determined based on original prevalence data and the estimated monthly recruitment deemed feasible by the participating European centers (18).

Patient and Public Involvement Statement

Two Patient Advocacy Organizations (PAOs) from Germany and French participate in the PROFA study. The PAOs are involved in (i) the final conceptualization phase of the study before starting the data assessment to receive added value by confirming the existing and

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identifying further patient priorities of the PROFA study and by bringing the patient perspective into the study design; (ii) 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; (iii) 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 policy-makers, regulators, and other patient organizations. 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 centers. 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 (QMS) 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 assessment include a broad range of measures, capturing patient-reported and psychosocial outcomes, clinical parameters and healthcare utilization indicators. Table 2 gives an overview of all instruments and the administration location.

The baseline assessment via interviews at the study centers includes socio-demographics 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 center data. The database will be implemented by the clinician in charge or an authorized staff member who has been granted access and modification rights to the database.

After the study center assessment, patients are given access to the Atom5™ Aparito m-health app and downloaded by patients. The study center 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 six months. The participants will complete a test survey over the app under the supervision of a clinician.

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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 & time of diagnosis, further medical diagnoses, disability stage, drug consumption, medication, general examination	Study centre[1]
Measures of clinical outcomes		
SARA	Ataxia Severity	Study centre[1]
SARA^{home}	Ataxia Severity	Remotely via App[2]
INAS	Non-ataxia signs/ symptoms	Study centre[1]
FARS-ADL	Subscale for the dimension Activity of daily living of the Friedreich ataxia rating scale	Remotely via App[2]
CCAS	Cognitive disability in ataxia	Study centre[1]
Measures of patient-reported outcomes		
EQ-5D-**5L**	Health-related quality of life (generic), adult version	Remotely via App[2]
EQ-5D-Y-5L	Health-related quality of life (generic), youth version	Remotely via App[2]
PROM-Ataxia Short Form	Health-related quality of life (disease-specific)	Remotely via App[2]
Measures of psychosocial outcomes		
COMATAX	Disabilities in communication	Remotely via App[2]
Speech records	Rate of speech	Remotely via App[2]
VHI-30	Subjectively experienced voice disorders	Study centre[1] and remotely via App[2]
SSQ-12	Speech perception across multiple domains	Study centre[1] and remotely via App[2]
WEMWBS	Psychological well-being	Remotely via App[2]
Digit triplet test	Early detection of hearing loss	Study centre[1]
Brief-COPE	Coping strategies for stressful events	Study centre[1]
Measure of health resource outcomes		
Health utilization questionnaire based on FIMA and RUD	Utilization of health care services, informal care, caregiver productivity losses, adverse health events	Remotely via App[2]

[1]REDCap; [2] Atom5™ App from Aparito (Wrexham); SARA^{home}: Scale for the assessment and rating of ataxia at home; EQ-5D-(Y)-5L: EuroQol five Dimensions Questionnaire, PROM-Ataxia short: Patient-Reported Outcome Measure of Ataxia; COMATAX: Communication in Ataxia; WEMWBS: Warwick-Edinburgh Mental Well-Being Scale; VHI-30: Voice Handicap Index; SSQ-12: Speech, Spatial and Qualities of Hearing Scale short version; FIMA: Questionnaire for health-related resource use; RUD: Ressource Utilization

This is essential to ensure a high-quality data assessment, familiarize 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 center will be handed out to participants. All study center physicians participating in the study will receive standardized training and a handbook with information about the data collection and instructions about using the REDCap study center database and the m-health app assessment.

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Subsequently, participants will self-complete tests and surveys daily to monthly for six 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 also be a better environment for patients than general study center visits, where patients have long travels and waiting times, which could cause distress, especially for FA patients.

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Table 3: Sequence of App-based instruments

Day	SARA^{home}	EQ-5D-(Y)-5L	PROM-Ataxia Short Form	COMATAX	WEMWBS	VHI	SSQ12	Speech records	Resource Utilization
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 three consecutive days; ✓administered only once; SARA^{home}: Scale for the assessment and rating of ataxia (home version); EQ-5D-(Y)-5L: EuroQol five Dimensions Questionnaire; PROM-Ataxia Short Form: Patient-Reported Outcome Measure of Ataxia; COMATAX: Communication in Ataxia; WEMWBS: Warwick-Edinburgh Mental Well-Being Scale; VHI: Voice Handicap Index; SSQ12: Speech, Spatial and Qualities of Hearing Scale short version; HUQ: Health Utilization Questionnaire

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

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youth version will be administered as recommended in the population of ages 12 to 16. 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 ten items (23). The instrument is the short version of the valid and reliable 70-item PROM-Ataxia questionnaire, developed based on cerebellar ataxia patients' symptom experiences and influenced activities (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 Scale for the assessment and rating of ataxia (SARA) (24), the Inventory of Non-Ataxia Signs (INAS) (25), the Activities of daily living assessment as part of the Friedreich ataxia 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 centers. 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. Centralized 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 (SSQ12) (32, 33), Speech records (repetition on the days of the week during 30 seconds), 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) (38, 39).

To assess self-rated disabilities in communication, the new instrument COM-ATAX 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 FA patients, informal and professional caregivers will be conducted. Within these focus groups, participants should directly mention the communication difficulties that affect their psychosocial health. A

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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 utilization 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 two-monthly administration, we reduced the recall period from three (in the original FIMA) to two months. Informal care and caregiver's productivity losses will be assessed with items of the RUD Lite measure, administering questions about the utilization of caregiver support for activities of daily living and instrumental activities of daily living and caregivers' short- and long-term productivity losses (41). Unlike the original, we will ask FA patients about the informal caregivers' situation instead the informal caregivers themselves. Additionally, specific adverse health events will be assessed. These items can be categorized into disease-, relationship- 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 FA patients (evaluation study).

Validation of the m-health remote app

We will use descriptive statistics to analyze 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 hypothesize 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.

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Further, we will analyze 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, SSQ12, 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 analyze the instruments regarding their distributional properties, reliability, validity, responsiveness and ability to distinguish between groups by sociodemographic (e.g. age, gender) and clinically specific components (e.g. FA disease stages).

Economic burden: Healthcare resource use and costs

Healthcare service utilization, informal care provision, and productivity losses will be monetarized using a standardized unit, opportunity, and friction cost approach, respectively, and evaluated from a societal perspective. Costs will be analyzed 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 (e.g. speech& 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-VAS. 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 (three consecutive days) and analyze the EQ-5D-5Ls spread and variability. These findings will be compared with clinically significant differences in the $SARA^{home}$, using descriptive statistics. We hypothesize 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

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use generalized 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 SSQ12 scores (32, 33) will be analyzed 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 (30 seconds of continued speech "days of the weeks") and the auditory screening results will be correlated to the self-survey of dysarthria (VHI), hearing loss (SSQ12), 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 utilization patterns of health resources, like the utilization of evidence-based treatment and care, and its costs, patients' HRQoL and the psychosocial impact of communication difficulties will be analyzed using multivariate linear and logistic regression models.

Expected results

The PROFA study will provide a comprehensive and better understanding of the disease burden of FA patients' everyday life, determinants of psychosocial health and HRQoL, as well as a detailed description of specific health events, healthcare service utilization 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 FA patients' HRQoL and psychosocial health. 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 will and patients' HRQoL will be highly relevant for designing targeted, quality-controlled, standardized treatment and rehabilitation programs that aim to improve patients' health.

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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 FA patients' outcomes. 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 utilization 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 FA patients' daily life. 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 underrepresented 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 programs and future clinical and health care research trials. All of this can potentially improve the current treatment, care and living situation of FA patients and their families.

3 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. Furthermore, the study is currently under review in the Clinical Trials.cov Register. All participants and parents of participants under the age of 18 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.

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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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Competing interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author Contributions

BM, TKlockgether, MGE, FX, SB conceptualised and designed the study. MGE, KR, TKlopstock, LS, SBoesch, SBorel organized the implementation in the respective study centers for recruiting patients and collecting data. MS, 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 further authors read, revised and approved the final manuscript.

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Legend

Figure 1: PROFA study design (simplified)

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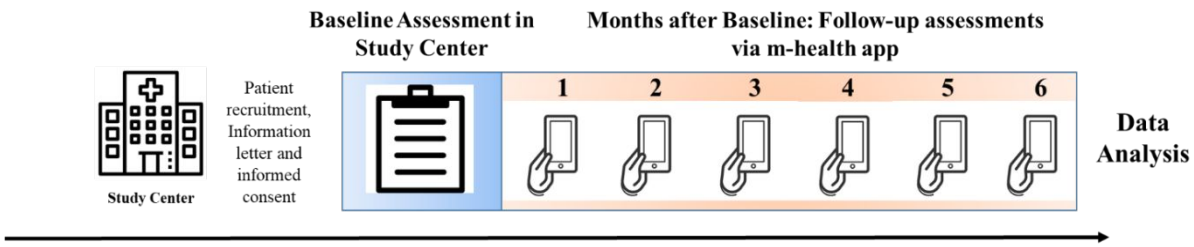
Figure 1: PROFA study design (simplified)



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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-11
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-11
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-13
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	11-13
Bias	9	Describe any efforts to address potential sources of bias	3
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	13-15
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	13-15
		(*b*) Describe any methods used to examine subgroups and interactions	14-15
		(*c*) Explain how missing data were addressed	Study Protocol na
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	Study Protocol na
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Study Protocol na
		(b) Give reasons for non-participation at each stage	Study Protocol na
		(c) Consider use of a flow diagram	Study Protocol na
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Study Protocol na
		(b) Indicate number of participants with missing data for each variable of interest	Study Protocol na
		(c) Summarise follow-up time (eg, average and total amount)	Study Protocol na
Outcome data	15*	Report numbers of outcome events or summary measures over time	Study Protocol na
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Study Protocol na
		(*b*) Report category boundaries when continuous variables were categorized	Study Protocol na
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Study Protocol na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Study Protocol na
Discussion			
Key results	18	Summarise key results with reference to study objectives	15-16
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Study Protocol na
Generalisability	21	Discuss the generalisability (external validity) of the study results	Study Protocol na
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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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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Secondary Subject Heading:	Health economics, Health services research, Patient-centred medicine
Keywords:	HEALTH ECONOMICS, Quality of Life, Neurology < INTERNAL MEDICINE, Surveys and Questionnaires

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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

Maresa Buchholz[1]*, Niklas Weber[1], Stephanie Borel[2], Sabrina Sayah[2], Feng Xie[3], Jörg Schulz[4,*], Kathrin Reetz[4,5], Sylvia Boesch[6], Thomas Klopstock[7], Ivan Karin[7], Ludger Schöls[8], Marcus Grobe-Einsler[9], Thomas Klockgether[9], Elin Haf Davies[10], Madleine Schmeder[11], Andreas Nadke[12], Bernhard Michalowsky[1]

1. German Center for Neurodegenerative Diseases (DZNE), Site Rostock/ Greifswald, Greifswald, Germany.

2. Sorbonne University, Paris Brain Institute (ICM - Institut du Cerveau), INSERM, CNRS, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France.

3. McMaster University, Department Health Research Methods, Evidence and Impact, Hamilton, Canada.

4. Klinik für Neurologie, RWTH Aachen, Aachen, Germany.

5. JARA Institute Molecular Neuroscience and Neuroimaging, RWTH Aachen & Forschungszentrum Jülich, Aachen, Germany

6. Klinik für Neurologie, Medizinische Universität Innsbruck, Innsbruck, Austria.

7. Friedrich-Baur-Institut an der Neurologischen Klinik und Poliklinik, LMU München, Munich, Germany.

8. Neurologische Klinik und Hertie-Institut für Klinische Hirnforschung, Universitätsklinik Tübingen, Tübingen, Germany.

9. German Center for Neurodegenerative Diseases (DZNE) site Bonn, Bonn, Germany.

10. Aparito Ltd, Wrexam, Wales.

11. Association Française de l'Ataxie de Friedreich, Hirson, France.

12. Deutsche Heredo-Ataxie-Gesellschaft e.V., Stuttgart, Germany.

*** Correspondence:**
Maresa Buchholz, German Center for Neurodegenerative Diseases e.V., Ellernholzstraße 1-2, 17487 Greifswald, Germany, maresa.buchholz@dzne.de

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Abstract

Introduction: Friedreich ataxia (FA) is the most common hereditary ataxia in Europe, characterized by progressively worsening movement and speech impairments with a typical onset before the age of 25. 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 mobile-health app.

Methods and analysis: The PROFA Study is a prospective observational study. FA patients (n=200) will be recruited at six European study centers (Germany, France, and Austria). We will interview patients at baseline in the study center 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 the monthly basis on the app for six months. Our study aims to i) validate measurements of HRQoL and psychosocial health, ii) assess the usability of the mobile-health app, and iii) use descriptive and multivariate statistics to analyze 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 FA patients' outcomes.

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 PAOs.

ClinicalTrials.gov Identifier: NCT05943002

Strength 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.

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- Assessing the acceptability, feasibility, and usability of a mobile-health (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 for 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.

Keywords: Rare diseases, Friedreich ataxia, patient-reported outcomes, health economics, m-health app assessment, speech and hearing disabilities, health and informal care

Words: 4.069

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1 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 eight and 15. Thus, neurodegenerative movement disorder often affects people in early adulthood (4). Muscle weakness, imbalance, poor coordination, sensory loss, and speech problems (dysarthria) characterize 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 stabilize FA patients' functional status 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 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 utilization 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 utilization 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, seven hours per week of informal care to support patients in their activities of daily living. Approximately every fourth of informal caregivers is unemployed due to FA. Thus, informal care and caregivers' productivity losses cause further indirect costs (14). Studies in neurodegenerative diseases, such as ALS, Parkinson, Huntington's Disease or dementia, report an increasing disease severity and an

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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 utilization of healthcare services.

FA patients 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 interrelationships among psychosocial, patient-reported and economic aspects need to be analyzed 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 m-health app and a momentary data collection on a daily to monthly basis over six months to assess patient-reported and psychosocial outcomes as well as the economic impact of FA. The main study objectives are as follows:

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Validation part of the study
(1) Assessing the acceptability, feasibility, and usability of an m-health app Atom5™, to collect real-time health-related quality of life, economic, and psychosocial data from patients with FA.
(2) Validation of a new measure of hearing and speech disabilities' impact on patients' psychosocial health (COMATAX).
(3) Validation of the generic 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 utilization and costs for patients with FA from a societal perspective that includes medical, care, and informal care costs and analyzing 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 utilization patterns of healthcare resource use (evidence-based treatment and care), HRQoL, and psychosocial health.

2 METHODS AND ANALYSIS

Study design

The PROFA study is a multi-centric, prospective, observational study. Eligible patients will be recruited from six study centers 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 centers and multiple follow-up remote online momentary data assessment via an m-health app on a daily to monthly basis for six 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.

*** Please insert here Figure 1: PROFA study design (simplified) ***

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 centers in Germany, France, and Austria, participants (or legal representatives) will be verbally informed about the study objectives and procedures by a study center physician, receive an information sheet, and asked to provide informed consent. Participants under the age of 18 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 centers 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

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 centers that are also participating in the PROFA study have recruited n= 200 FA patients. Based on the recruitment of the EFACTS study we assume an initial sample size of 200 patients for six study centers within a one-year timeframe. This number was determined based on original prevalence data and the estimated monthly recruitment deemed feasible by the participating European centers (18).

Patient and Public Involvement Statement

Two Patient Advocacy Organizations (PAOs) from Germany and French participate in the PROFA study. The PAOs are involved in (i) the final conceptualization phase of the study before starting the data assessment to receive added value by confirming the existing and

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identifying further patient priorities of the PROFA study and by bringing the patient perspective into the study design; (ii) 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; (iii) 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 policy-makers, regulators, and other patient organizations. 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 centers. 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 (QMS) 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 assessment include a broad range of measures, capturing patient-reported and psychosocial outcomes, clinical parameters and healthcare utilization indicators. Table 2 gives an overview of all instruments and the administration location.

The baseline assessment via interviews at the study centers includes socio-demographics 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 center data. The database will be implemented by the clinician in charge or an authorized staff member who has been granted access and modification rights to the database.

After the study center assessment, patients are given access to the Atom5™ Aparito m-health app and downloaded by patients. The study center 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 six months. The participants will complete a test survey over the app under the supervision of a clinician.

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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 & time of diagnosis, further medical diagnoses, disability stage, drug consumption, medication, general examination	Study centre[1]
Measures of clinical outcomes		
SARA	Ataxia Severity	Study centre[1]
SARA^{home}	Ataxia Severity	Remotely via App[2]
INAS	Non-ataxia signs/ symptoms	Study centre[1]
FARS-ADL	Subscale for the dimension Activity of daily living of the Friedreich ataxia rating scale	Remotely via App[2]
CCAS	Cognitive disability in ataxia	Study centre[1]
Measures of patient-reported outcomes		
EQ-5D-5L	Health-related quality of life (generic), adult version	Remotely via App[2]
EQ-5D-Y-5L	Health-related quality of life (generic), youth version	Remotely via App[2]
PROM-Ataxia Short Form	Health-related quality of life (disease-specific)	Remotely via App[2]
Measures of psychosocial outcomes		
COMATAX	Disabilities in communication	Remotely via App[2]
Speech records	Rate of speech	Remotely via App[2]
VHI-30	Subjectively experienced voice disorders	Study centre[1] and remotely via App[2]
SSQ-12	Speech perception across multiple domains	Study centre[1] and remotely via App[2]
WEMWBS	Psychological well-being	Remotely via App[2]
Digit triplet test	Early detection of hearing loss	Study centre[1]
Brief-COPE	Coping strategies for stressful events	Study centre[1]
Measure of health resource outcomes		
Health utilization questionnaire based on FIMA and RUD	Utilization of health care services, informal care, caregiver productivity losses, adverse health events	Remotely via App[2]

[1]REDCap; [2] Atom5™ App from Aparito (Wrexham); SARA^{home}: Scale for the assessment and rating of ataxia at home; EQ-5D-(Y)-5L: EuroQol five Dimensions Questionnaire, PROM-Ataxia short: Patient-Reported Outcome Measure of Ataxia; COMATAX: Communication in Ataxia; WEMWBS: Warwick-Edinburgh Mental Well-Being Scale; VHI-30: Voice Handicap Index; SSQ-12: Speech, Spatial and Qualities of Hearing Scale short version; FIMA: Questionnaire for health-related resource use; RUD: Ressource Utilization

This is essential to ensure a high-quality data assessment, familiarize 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 center will be handed out to participants. All study center physicians participating in the study will receive standardized training and a handbook with information about the data collection and instructions about using the REDCap study center database and the m-health app assessment.

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Subsequently, participants will self-complete tests and surveys daily to monthly for six 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 also be a better environment for patients than general study center visits, where patients have long travels and waiting times, which could cause distress, especially for FA patients.

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Table 3: Sequence of App-based instruments

Day	SARA^{home}	EQ-5D-(Y)-5L	PROM-Ataxia Short Form	COMATAX	WEMWBS	VHI	SSQ12	Speech records	Resource Utilization
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 three consecutive days; ✓administered only once; SARA^{home}: Scale for the assessment and rating of ataxia (home version); EQ-5D-(Y)-5L: EuroQol five Dimensions Questionnaire; PROM-Ataxia Short Form: Patient-Reported Outcome Measure of Ataxia; COMATAX: Communication in Ataxia; WEMWBS: Warwick-Edinburgh Mental Well-Being Scale; VHI: Voice Handicap Index; SSQ12: Speech, Spatial and Qualities of Hearing Scale short version; HUQ: Health Utilization Questionnaire

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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

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youth version will be administered as recommended in the population of ages 12 to 16. 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 ten items (23). The instrument is the short version of the valid and reliable 70-item PROM-Ataxia questionnaire, developed based on cerebellar ataxia patients' symptom experiences and influenced activities (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 Scale for the assessment and rating of ataxia (SARA) (24), the Inventory of Non-Ataxia Signs (INAS) (25), the Activities of daily living assessment as part of the Friedreich ataxia 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 centers. 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. Centralized 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 (SSQ12) (32, 33), Speech records (repetition on the days of the week during 30 seconds), 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) (38, 39).

To assess self-rated disabilities in communication, the new instrument COM-ATAX 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 FA patients, informal and professional caregivers will be conducted. Within these focus groups, participants should directly mention the communication difficulties that affect their psychosocial health. A

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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 utilization 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 two-monthly administration, we reduced the recall period from three (in the original FIMA) to two months. Informal care and caregiver's productivity losses will be assessed with items of the RUD Lite measure, administering questions about the utilization of caregiver support for activities of daily living and instrumental activities of daily living and caregivers' short- and long-term productivity losses (41). Unlike the original, we will ask FA patients about the informal caregivers' situation instead the informal caregivers themselves. Additionally, specific adverse health events will be assessed. These items can be categorized into disease-, relationship- 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 FA patients (evaluation study).

Validation of the m-health remote app

We will use descriptive statistics to analyze 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 hypothesize 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.

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Further, we will analyze 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, SSQ12, 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 analyze the instruments regarding their distributional properties, reliability, validity, responsiveness and ability to distinguish between groups by sociodemographic (e.g. age, gender) and clinically specific components (e.g. FA disease stages).

Economic burden: Healthcare resource use and costs

Healthcare service utilization, informal care provision, and productivity losses will be monetarized using a standardized unit, opportunity, and friction cost approach, respectively, and evaluated from a societal perspective. Costs will be analyzed 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 (e.g. speech& 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-VAS. 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 (three consecutive days) and analyze the EQ-5D-5Ls spread and variability. These findings will be compared with clinically significant differences in the $SARA^{home}$, using descriptive statistics. We hypothesize 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

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use generalized 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 SSQ12 scores (32, 33) will be analyzed 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 (30 seconds of continued speech "days of the weeks") and the auditory screening results will be correlated to the self-survey of dysarthria (VHI), hearing loss (SSQ12), 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 utilization patterns of health resources, like the utilization of evidence-based treatment and care, and its costs, patients' HRQoL and the psychosocial impact of communication difficulties will be analyzed using multivariate linear and logistic regression models.

Expected results

The PROFA study will provide a comprehensive and better understanding of the disease burden of FA patients' everyday life, determinants of psychosocial health and HRQoL, as well as a detailed description of specific health events, healthcare service utilization 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 FA patients' HRQoL and psychosocial health. 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 will and patients' HRQoL will be highly relevant for designing targeted, quality-controlled, standardized treatment and rehabilitation programs that aim to improve patients' health.

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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 FA patients' outcomes. 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 utilization 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 FA patients' daily life. 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 underrepresented 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 programs and future clinical and health care research trials. All of this can potentially improve the current treatment, care and living situation of FA patients and their families.

3 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;

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Paris: Comité de Protection des Personnes Est III, ethical vote number: 2023-A00315-40). Furthermore, the study is currently under review in the Clinical Trials.cov Register. All participants and parents of participants under the age of 18 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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Competing interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author Contributions

BM, TKlockgether, MGE, FX, SB conceptualised and designed the study. MGE, KR, TKlopstock, LS, SBoesch, SBorel organized the implementation in the respective study centers for recruiting patients and collecting data. MS, 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 read, MB, NW, SBorel, SS, FX, JS, KR, SBoesch, TKlopstock, IK, LS, MGE, TKlockgether, EHD, MS, AN, BM, revised and approved the final manuscript.

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Legend

Figure 1: PROFA study design (simplified)

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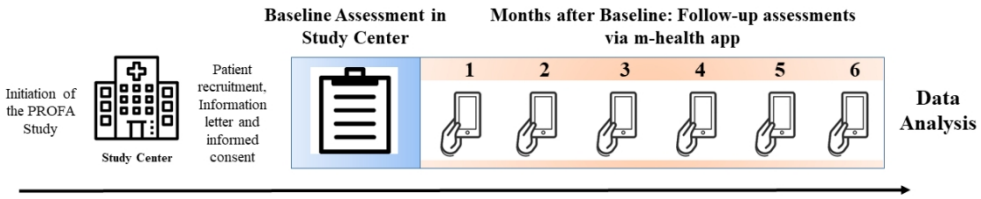

Figure 1: PROFA study design (simplified)

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-11
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-11
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-13
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	11-13
Bias	9	Describe any efforts to address potential sources of bias	3
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	13-15
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	13-15
		(*b*) Describe any methods used to examine subgroups and interactions	14-15
		(*c*) Explain how missing data were addressed	Study Protocol na
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	Study Protocol na
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Study Protocol na
		(b) Give reasons for non-participation at each stage	Study Protocol na
		(c) Consider use of a flow diagram	Study Protocol na
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Study Protocol na
		(b) Indicate number of participants with missing data for each variable of interest	Study Protocol na
		(c) Summarise follow-up time (eg, average and total amount)	Study Protocol na
Outcome data	15*	Report numbers of outcome events or summary measures over time	Study Protocol na
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Study Protocol na
		(*b*) Report category boundaries when continuous variables were categorized	Study Protocol na
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Study Protocol na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Study Protocol na
Discussion			
Key results	18	Summarise key results with reference to study objectives	15-16
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Study Protocol na
Generalisability	21	Discuss the generalisability (external validity) of the study results	Study Protocol na
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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