Title: A Longitudinal Laboratory and Real-world Study of Gait and Balance in People with Friedreich's Ataxia

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Contents

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Chief Investigator

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Date ……

Site Principal Investigator (if different to above)

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Signature ……

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Study Summary Information

Study Title	A Longitudinal Laboratory and Real-world Study of Gait and Balance in People with Friedreich's Ataxia
Short Title/Acronym	Friedreich's Ataxia: Balance & Gait
Summary of Design	Prospective observational study
Summary of Participant Population	Patients aged between 14 and 65 years with genetically confirmed Friedreich's ataxia
Planned Sample Size	16
Per Participant Duration	12 months
Proposed Overall Duration	24 months
Study Aim	To identify outcome measures that can reliably detect disease progression and validate instrumented measures against traditional clinical rating scales for Friedreich's ataxia.

Abbreviations

FA – Friedreich's ataxia

ABC - Activities-specific Balance Confidence scale

Ax6 -Axivity triaxial accelerometer

BRAIN - BRadykinesia Akinesia INcoordination test

CI - Chief Investigator

CRF - Case Report Form

GCP - Good Clinical Practice

GP- General Practitioner

HRA - Health Research Authority

ICF - Informed Consent Form

INAS - Inventory of Non-Ataxia Signs

ISF - Investigator Site File

LPLV - Last Participant Last Visit

MRI - Magnetic resonance imaging

NJRO - Newcastle Joint Research Office

PI - Principal Investigator

PIS - Participant Information Sheet

PROMA - Patient-Reported Outcome Measure of Ataxia

QoL - Quality of Life

R&D - Research & Development

REC - Research Ethics Committee

SAE - Serious Adverse Event

SOP - Standard Operating Procedure

SUSAR - Suspected Unexpected Serious Adverse Reaction

TMF - Trial Master File

WCMR - Wellcome Centre for Mitochondrial Research

Study Summary

This is an observational pilot study that will investigate disease progression in patients with Friedreich's ataxia (FA) by evaluating gait and balance using laboratory-based assessments and traditional rating scales. The study is part of a collaboration between two leading research centres (Wellcome Centre for Mitochondrial Research, UK, and Hertie Institute for Clinical Brain Research and Centre for Integrative Neuroscience, Germany (Tübingen). Data collected at both centres (under separate protocols and separate regulatory permissions) will be combined as part of the analyses. However, this protocol relates to the UK study and data collection only.

Dominant phenotypes in FA include mixed sensory and cerebellar ataxia, pyramidal tract symptoms, and weakness, all significantly affecting gait and mobility. Current clinical rating scales used to determine the disease severity are limited by subjectivity, inter-rater variability, and lack of sensitivity to subtle changes in disease progression.

The study will utilize clinical rating scales, functional assessments, patient-reported outcomes, postural and gait analysis, and wearable technology. The assessment outcomes will be evaluated to make recommendations based on their sensitivity and reliability in measuring real-world mobility and progression in patients with FA.

Background

Friedreich's ataxia is the most common recessive ataxic disorder in Caucasian populations, and most patients are homozygous for GAA expansion in the frataxin gene (FXN). The median age of disease onset is around 11 years; however, a wide age range (2-78 years) has been reported. Patients with FA frequently exhibit complex neurological phenotypes characterized by mixed sensory and cerebellar ataxia, muscle weakness due to pyramidal tract involvement, and other symptoms such as scoliosis and optic atrophy.

A recent online survey of 342 respondents with different types of ataxia identified gait and balance problems as the main symptoms that clinical trials should address, especially in an ambulatory group (1). Clinical rating scales such as Scale for the Assessment and Rating of Ataxia (SARA) or FA-specific scales such as Friedreich's Ataxia Rating Scale (FARS) are commonly used in clinical practice and research studies to determine the severity of ataxia. Several natural history studies employing these scales have provided invaluable insights into the temporal disease pattern and progression in FA over yearly intervals. In FA, the disease progression follows a rapid trajectory, depending on the age of onset (2) compared to dominant spinocerebellar ataxias (3).

However, inherent limitations of using clinical rating scales include the semi-quantitative and subjective nature, inter-rater variability and lack of sensitivity to detect change over short time periods (e.g. 6-12 months), with ceiling effects (4). Also, the small effect size of studies using clinical rating scales as the primary outcome means a large sample size is required (5), which is a significant barrier to the delivery of clinical trials in FA. Therefore, selecting robust clinical outcome measures which are reliable and sensitive to change is fundamental to testing novel therapeutic compounds, especially in drug studies with duration of less than one year.

Instrumented balance and gait assessments are sensitive tools to capture spatial and temporal characteristics of mobility impairment. Gait parameters can robustly discern patients with several neurological conditions such as cerebellar ataxia (6) and Parkinson's disease (PD) from a healthy control group. Changes in gait can also be tracked objectively over time and provide a measure of disease progression, as shown in the PD population (7) and recently also in spinocerebellar ataxia (8). Compared to age-matched healthy controls, both paediatric (9, 10) and adult (11-13) FA patients have characteristic ataxic gait patterns: slower walking speeds, reduced cadence (meaning fewer steps per minute), shorter step and stride lengths, increased gait variability, increased stance phase, and double limb support duration, and increased displacement of the centre of mass. Several of these gait parameters significantly correlated with disease severity in FA, measured by ICARS (13), FARS (10, 11), and SARA (9). A longitudinal study of 11 paediatric FA patients identified only certain kinematic and kinetic profiles (knee extension during the stance phase) exhibiting significant changes over a 12-month interval (9). Vasco and colleagues concluded that gait impairment in FA patients results from the complex interaction between cerebellar dysfunction and somatosensory loss, compromising balance control and multi-joint coordination (9). However, it is currently not known whether instrumented evaluation of balance and gait is sensitive to detecting longitudinal changes in ataxia severity in adult FA patients.

Evaluating adult FA patients who have longer disease duration is important, as they may have developed adaptive / compensatory changes, compared to the paediatric population. More recently, wearable sensors are emerging as promising tools for monitoring real-world mobility. Wearable sensors offer a number of advantages compared to laboratory-based assessments, including better tolerability, ecological validity and a more economical approach to patient monitoring, demonstrating huge translational potential to be incorporated in clinical practice in the future. Such an approach promotes inclusivity by enhancing access to healthcare and clinical management through remote monitoring (i.e. rural and underserved populations, and during the pandemic). Two recent publications have highlighted the feasibility and reliability of capturing discriminative gait outcomes in patients with spinocerebellar ataxia and other genetic subtypes using wearable sensors (inertial measurement units) in a supervised environment (14, 15) and real-life habitual environments (14), and these measures correlated with disease severity.

From these studies, it is indisputable that there is a need for more robust studies to compare the efficacy of different assessment tools in measuring the severity of gait and mobility in FA patients.

Objectives and Outcome Measures

The primary outcome measures are instrumented measures of balance and gait collected in a specialist gait laboratory. Data acquisition techniques include stabilometry (force plate analysis), instrumented walkway (GaitRite) and wearable sensors (Opal and Ax6).

Primary Objective

- Evaluate instrumented measures of balance and gait in a controlled setting (clinical research laboratory) repeatedly (three times in 12 months) in ambulatory patients (age 14-65 years) with FA to determine which outcomes are sensitive to disease progression.

Secondary Objectives

- Investigate the influence of sensor location and configuration (i.e. single sensor vs. multiple sensors) on the generation of balance and gait outcomes in a controlled setting (clinical research laboratory).
- Validate gait outcomes measured using the wearable sensors against a gold standard (instrumented walkway) in a controlled setting (clinical research laboratory)
- Determine the feasibility of monitoring real-world mobility (habitual activity and gait) in FA patients and explore whether these outcomes are more sensitive than traditional clinical rating scales and controlled laboratory-based assessments.

Study Design and Setting

This study is designed as an observational pilot study involving 16 FA patients (ages 14-65 years). It is sponsored by Newcastle University but will take place at The Newcastle upon Tyne Hospitals NHS Foundation Trust (study site). The study will involve participants visiting at three time-points (Baseline, Month-6, and Month-12).

This protocol is part of a larger collaborative project also involving data collected via a separate study undertaken and managed by the Hertie Institute for Clinical Brain Research and Centre for Integrative Neuroscience (Tubingen).

Data (in an anonymised and pseudo-anonymised form) from both studies will be shared between collaborators and combined for data analyses.

Study Procedures

Participant Identification

Participants will be identified via neurology, paediatric and cardiology clinics at the Newcastle upon Tyne Hospitals NHS Foundation Trust. The direct clinical care team (of which the research team are part) will review clinic lists to identify potentially eligible patients.

Potentially eligible patients will be sent a study invitation letter along with a copy of the relevant Participant Information Sheet (PIS) or will be contacted by telephone/in person by their direct clinical care team (i.e. during a routine clinic) and invited to participate. Patients who are sent an invitation letter by post may also be contacted by telephone after the letter has been sent to check that it has been received.

The study will also be advertised via the websites and social media channels of charities and patient groups (e.g. Ataxia UK) and any volunteering participant will be able to contact the study team for enquiries regarding the study.

Where the age of the eligible participant is 14 or 15-years-old (i.e. under 16), parents/carers with parental responsibility will be provided with information about the study and the opportunity to ask questions about the participation of their child. The potential paediatric participant will also be provided with a suitable Participant Information Sheet (PIS).

Screening and Informed Consent

Where potential participants indicate a willingness to be involved in the study they will be contacted via phone /virtually (via email or video-conferencing software such as Zoom and Microsoft Teams) to discuss participation and to ask any questions they may have. At this contact their eligibility will be ascertained.

Potential participants who are deemed to be eligible will be then invited to attend a study Baseline visit where eligibility will be formally documented and written informed consent obtained. The parent (or person with parental responsibility) of any participants aged 14 and 15 years will be asked to provide informed consent on behalf of their child.

All consent and assent forms will be checked and countersigned by the person who discussed the study with the participant. By countersigning the consent form, the individual confirms that they discussed the study with the potential participant and are confident that informed consent has been provided by the participant themselves.

As outlined above, parental consent will be sought on behalf of children aged under 16, however wherever possible (if considered appropriate by the parent/carer and the research team at site), written assent for participation will be sought from the child. If a child is considered capable of providing assent but is unwilling to provide this, they will not be recruited into the study

Children who turn 16 during their participation in the study will be re-consented as adults.

Once consent has been completed, and the form countersigned, study activities can commence. A copy of the signed Informed Consent/Assent Form will be given to the participant and a copy filed in their hospital records. Original signed consent forms will be stored in the Investigator Site File. A letter will be sent to the participant's general practitioner to inform them of their patient's participation in this study. A copy of this letter will be filed in the participant's hospital records.

An anonymised study pre-screening log will be kept which will include details of all individuals who are invited to participate and with whom study participation is discussed. This log will include the reason for screen failure (if applicable).

Eligibility Criteria

- Inclusion criteria

- Genetically confirmed FA
- Aged 14 to 65 years.
- Able to stand and walk unaided for at least 20m.
- Able to provide informed consent.
- Able to follow instructions and comply with the study protocol.
- Willing to wear a small sensor on the lower back for seven consecutive days
- No other known neurological or musculoskeletal disorder affecting balance and mobility.

- Exclusion criteria

- Lacking capacity to provide informed consent
- Enrolled in interfering therapy or clinical drug trial currently or within last three months
- Pregnancy at the time of enrolment

  Any other reason, which in the opinion of the recruiting investigator would preclude involvement in the study

- Withdrawal Criteria

- Participants have the right to withdraw from the study at any time. A member of the research team should try to ascertain the reason for withdrawal and document this reason within the participant's medical records.
- The Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:
    - Participant withdrawal of consent
    - Significant protocol deviation or non-compliance
    - Investigator's discretion that it is in the best interest of the participant to withdraw
    - An adverse event that renders the participant unable to continue in the study*
    - Termination of the study by the sponsor or funder

If participants are withdrawn from the study, the information already obtained up to point of withdrawal will be retained. To safeguard the rights of the participant, the minimum of personally-identifiable information possible will be used.

Participants who withdraw from the study at any point after Baseline will not be replaced.

*Please note, if the participant has a severe adverse reaction to the adhesive used to attach the wearable sensor- further use of wearable sensors in the home environment may be stopped however the participant will still be able to remain on the study and complete the other assessments.

Study Assessments and Data Collection

Each participant will undergo the following assessments at three visits (Baseline, at Month-6 +/- 2 weeks, and at Month-12 +/- 2 weeks). Unless specified otherwise, all activities will be conducted for all participants.

Biometric Assessments

- Demographics (age, sex, alcohol consumption, smoking status, ethnicity, education level, socio-economic status)
- Anthropometrics (weight, height, body mass index)
- Medical history and concomitant medications
- Physical examination and vital signs (including blood pressure, pulse rate, respiratory rate)
- Clinical review of medical records and collection of previous/existing results from the following
    - Disease onset and year of diagnosis
    - Molecular genetic test (specifically the number of GAA repeat in *FXN* gene or point mutation)
    - Neuroimaging (CT or MRI head)
    - Laboratory tests (e.g. HbA1c and CK)
    - Nerve conduction study and electromyography (evidence of neuropathy/ganglionopathy)
    - Cardiac investigations such as ECG, echo radiography and cardiac MRI where available

Clinical Rating Scales

- Friedreich ataxia rating Scale (FARS)
- Scale for Assessment and Rating of Ataxia (SARA)
- Inventory of non-ataxia signs (INAS)
- CCAS (Cerebellar Cognitive Affective/ Schmahmann Syndrome Scale)

Participant Reported Outcomes

(Participant Reported Outcomes may be completed online or on paper up one week before or after the visit date)

- PROMA (Patient Reported Outcome Measure of Ataxia)
- NeuroQoL
- SF-36 (36-Item Short Form Survey Instrument)
- ABC Scale (Activity-Specific Balance Confidence Scale)
- FES-I (Falls Efficacy Scale International)
- The Fatigue Severity Scale (FSS)

Functional Assessments

- 9-hole peg test (9HPT)
- BRadykinesia Akinesia INcoordination (BRAIN) test
- Functional gait assessment (FGA)

Evaluation of Postural Control, Gait and Habitual Physical Activity

Wearable sensors comprising of triaxial accelerometers and gyroscopes (Opal, Axivity AX6) will be attached to the lower back and ankles for assessments in a specialist gait laboratory.

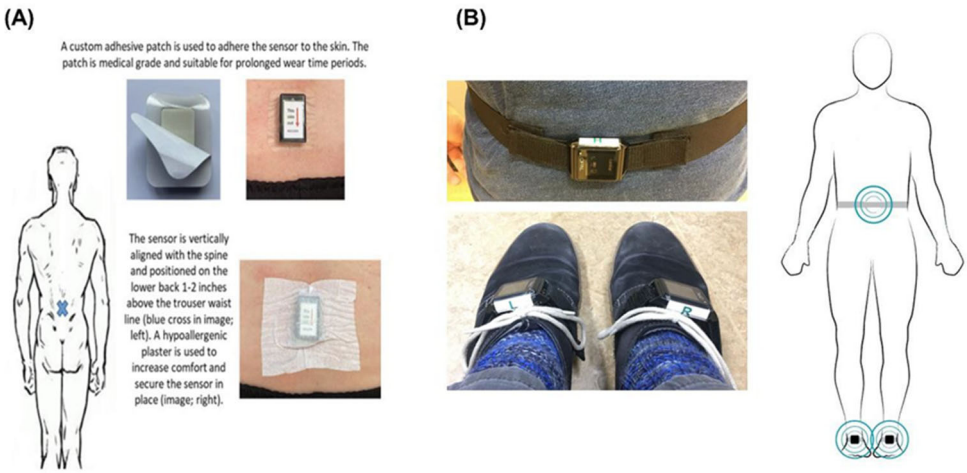

Figure. Wearable sensors. (A) Single sensor (Axivity AX6). (B) Opal sensors.

Postural control will be assessed with participants standing still under a variety of conditions that challenge balance:

- Normal stance (10-cm distance between heels), eyes open and eyes closed
- Narrow stance (feet together), eyes open and eyes closed
- Semi-tandem stance, eyes open

Participants will stand on a force platform for up to 60-seconds depending on functional mobility in each condition. Custom algorithms and manufacturer software will be used to derive balance outcomes from the force platform and wearable sensors respectfully. Outcomes extracted include centre of pressure area, displacement, path length, velocity, and root mean square.

Gait assessment will be completed using an instrumented walkway within a 10-m straight walkway. As functional mobility allows participants will be asked to complete:

- 6x 10-metre intermittent walks at a self-selected normal pace,
- 4x 10-metre walks at a self-selected fast pace
- 6-minute walk

Footfalls captured by the instrumented walkway will be processed and a battery of spatio-temporal gait outcomes will be extracted.

The following outcomes will be generated:

- Step length: distance in the direction of travel from the heel during foot contact to the contralateral heel during the next foot contact.
- Step time: duration from foot contact to contralateral foot contact
- Step velocity: step length divided by step time
- Stance time: duration from foot contact to when the foot is lifted off the ground
- Swing time: duration from when the foot is lifted off the ground to its next contact with the ground Step width: perpendicular distance between the heel (foot contact) and the direction of travel of the contralateral foot.

The mean, variability, and asymmetry of gait characteristics will be calculated. Custom algorithms developed at Newcastle University and Tubingen will be used to extract the same spatio-temporal gait outcomes outlined above (barring step width and step width variability) from the wearable sensors.

The gait assessments within the gait lab will be captured on video for the purposes of data veracity (to check for any anomalies in the data) during the processing/data analysis phase.

Habitual physical activity (real world activity) in the community will be measured by using a non-intrusive sensor (Axivity Ax6) on the lower back for seven consecutive days. A custom medical grade fixing is used to adhere the sensor to the skin (figure above). Previously tried and tested documents containing information and guidance will be provided to participants. The sensor will be set to pre-record for seven consecutive days to ensure a representative window of activity covering both weekday and weekend activity is obtained and given to the participant at the end of the laboratory session.

Following completion of recording, participants will return the sensor using a pre-paid, tracked envelope. Data will be downloaded from the sensor for processing. Outcomes of interest include daily time spent supine, sitting and moving as well as specific features of gait as outlined above (i.e. including walking speed, gait variability and asymmetry). We will compare this one sensor approach with the 3-sensor approach in the real-world assessment performed in Tubingen.

Collection of Feedback from Participants

In addition to the assessments conducted above, at the final study visit (Month-12) participants will be asked to provide feedback on their participation in the study. This will include their overall experience of the study and will also include discussion of any obstacles or challenges around use of wearable sensors. Information obtained from this feedback will be used to improve future studies.

Schedule of Events

	Assessments	Baseline	Month-6 (+/ -2 weeks)	Month-12 (+/ -2 weeks)
	Eligibility Confirmation	X		
	Informed Consent	X		
	Re-confirmation of Consent (verbal)		X	X
Biometric Assessments	Demographics	X	X	X
	Anthropometrics	X	X	X
	Medical History & Concomitant Medications	X	X	X
	Review of Existing Medical Records	X	X	X
	Vital Signs	X	X	X
	Physical Examination	X	X	X
Clinical Rating Scales	FARS	X	X	X
	SARA	X	X	X
	INAS	X	X	X
	CCAS	X	X	X
Participant Reported Outcomes	PROMA	X	X	X
	NeuroQOL	X	X	X
	SF-36	X	X	X
	ABC Scale	X	X	X
	FSS	X	X	X
	FES-I	X	X	X
Functional Assessments	9HPT	X	X	X
	BRAIN	X	X	X
	FGA	X	X	X
Evaluation of Gait and Postural Control	Static balance (stabiliometry) assessment [Force plates and wearable sensors (Opal and Ax6)]	X	X	X
	10 MWT; Self-selected and Fast Pace [GAITRite and Wearable Sensors (Opal and Ax6)]	X	X	X
	6 Minute Walk [GAITRite & Wearable Sensors (Opal & Ax6)]	X	X	X
	Wearable Sensors (Ax6) in Free-Living Environment (for 7 days post-visit)	X	X	X
	Adverse Event Reporting	X	X	X
	Feedback from Participants			X

Note: Participant reported outcome measures are shaded in grey.

End of study

The end of study for each participant will be completion of their Month-12 visit assessments (including collection of real-world activity data via wearable sensor for seven days post visit).

The overall end of study will be defined as the last participant last visit (LPLV). However, analyses of study data will continue after this point.

Statistics

Outcomes generated from clinical rating scales and questionnaires will be collated into a single dataset for subsequent statistical analysis.

Data from this study will also be combined with data provided by Tubingen University collected as part of a separate study utilising a similar protocol.

Determining which outcomes (clinical rating scales, laboratory and real-world monitoring of mobility) are sensitive to disease progression will be achieved by assessing change over time across the 3 time points using ANOVA.

We will determine the influence of sensor location (lower back vs. ankles) and configuration (single vs. multiple) on gait and balance outcomes by statistically comparing effect sizes of sensitivity to ataxia severity in cross-sectional and longitudinal analyses. We will also assess the test-retest reliability.

Gait outcomes derived from the wearable sensors will be validated against a gold standard (instrumented walkway) by quantifying the bias, intraclass coefficient and limits of agreement.

Correlations will be used to compare real-world mobility outcomes to traditional clinical rating scales and controlled laboratory-based mobility assessments.

Data analysis will be supported by the biostatistician at the WCMR.

Monitoring, Audit, and Inspection

The study may be subject to audit or monitoring by representatives of the Sponsor, Newcastle Hospitals, or inspection by regulatory authorities. Each investigator will permit study-related monitoring, audits and regulatory inspection including access to all essential documents and source data relating to the study. The site research team will follow local standard regulatory and quality assurance practices.

Adverse Event Reporting

Information on the participant's general health throughout the study will be collected and recorded in the participant's medical notes as part of the medical history data collection. However, due to the non-interventional nature of this study, only adverse events which directly relate to study procedures will be recorded as study adverse events.

Such adverse events will be documented in the participant medical records, recording causality and severity in addition to details of the event and will also be recorded on the study adverse event log held in the Investigator Site File (ISF). Copies of this log will be forwarded to Sponsor on a periodic basis for filing in the Trial Master File (TMF).

A Serious Adverse Event (SAE) for this study will be defined as an adverse event (as defined above) which meets any of the following criteria:

• Results in death

• Is life-threatening*

• Requires inpatient hospitalisation or prolongation of existing hospitalisation

• Results in persistent or significant disability/incapacity

• Consists of a congenital anomaly or birth defect

• Other important medical events that jeopardise the participant or require intervention to prevent one of the above consequences

*Life-threatening refers to an event in which the participant was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Any events which meet the above criteria, but which are not directly related to study visit procedures will not be considered to be SAEs. In the event of a Serious Adverse Event (SAE), the sponsor, Newcastle University will be notified immediately by email (within 24 hours of site awareness of the event) and the following details provided:

- Participants Unique Study ID number
- Event Title and Description (including details of severity)
- Expedited Reporting Criteria
- Date of Event Onset
- Date of Site Awareness
- Causality (i.e., whether related to study participation or study procedures)
- Expectedness (if related to a study procedure whether this is an 'expected' event)
- Action Taken
- Outcome/Status
- Resolution Date (if applicable)

The information will need to be confirmed by the PI or delegated investigator who is medically qualified. If complete information is not available or if a PI/Investigator cannot be obtained within 24 hours, the SAE report should be submitted as incomplete in the first instance and the missing details provided at the earliest opportunities.

SAEs will be followed up until resolution or until stabilisation (if complete resolution is not anticipated) and updated reports should be provided to the sponsor as required until resolution.

All SAEs will be recorded in the participant medical notes and recorded on the study adverse event logs held in the ISF and TMF. Any SAE notification emails- including updated notifications, should be retained in the ISF at site and will also be retained in the TMF.

Any SAEs that are related to a study procedure/visit and that are classified as unexpected will be reported to the Research Ethics Committee by the sponsor.

Abnormal Results or Issues of Concern

Any abnormal results or issues of concern identified during study visits and assessments will be referred to the Principal Investigator for discussion with the participant's routine clinical care team.

Ethical and Regulatory Considerations

The study will be conducted in accordance with sponsor and NHS site SOPs and ICH GCP.

The CI will obtain a favourable ethical opinion from an NHS Research Ethics Committee (REC) prior to the start of the study. All parties will conduct the study in accordance with this ethical opinion.

Amendments to the Study

It is the responsibility of the Sponsor to determine if an amendment is substantial or not and study procedures must not be changed without the mutual agreement of the CI and Sponsor. Substantial amendments will be submitted to the REC and Health Research Authority (HRA) and will not be implemented until approvals from both are in place.

Non-substantial amendments will be submitted to the HRA and will not be implemented until acknowledgement, or authorisation (if applicable) is received.

Notification of Serious Breaches to GCP and/or the Protocol

A serious breach is a breach which is likely to effect to a significant degree –

a) the safety or physical or mental integrity of the subjects of the study; or

b) the scientific value of the study

The Sponsor must be notified immediately of any incident that may be classified as a serious breach. The Sponsor will notify the NHS REC within the required timelines in accordance with the relevant Sponsor SOPs.

Deviations

Protocol deviations (intentional or unintentional) or deviations from GCP will be reported to the PI immediately and will be escalated to Sponsor as required. Deviations will be documented in the ISF alongside details of the response to the deviation and any corrective or preventative measures introduced.

Peer Review

This study is funded by the French Friedreich's Ataxia Association (A.F.A.F.) and therefore has been subject to peer review during the funding award process.

Data Management

Data Collection Tools and Source Documentation Identification

Completed study consent forms will be held in the ISF at the study site. Copies will be held in the participant's medical records.

Source data for this study will consist of annotations in the participant medical records, study specific researcher and clinician assessment tools, completed participant questionnaires, study data entered directly onto the study REDCap database, instrumented gait analysis data captured on specific software within the Gait Laboratory (including video recordings from the gait lab), and data downloaded from wearable sensors.

Completed study questionnaires and researcher/clinician assessment tools completed on paper will be stored in the ISF.

Information held in medical notes or within NHS electronic reporting systems will identify participants by name, DOB and other identifiers routinely used at the site (i.e. hospital number). Such identifiers will be removed when this data is provided to Sponsor or added to the study database and instead participants will be identified by their unique study ID number.

Any data collected directly via REDCap, study specific questionnaires and assessment tools which do not form part of the medical record, and data collected during gait analyses (including from wearable sensors), will be pseudo-anonymised (identifying participants via their study ID only).

Data collected on paper or in the medical record will be transcribed from the source data directly onto REDCap and combined with the data directly entered onto REDCap directly.

Data collected in the gait laboratory and via wearable sensors will be held separately and will not be entered to REDCap however certain limited gait data may be uploaded to REDCap at a later date. The video data captured within the gait lab will include facial features and therefore will be classed as identifiable. These videos will be stored securely at the gait laboratory with the other gait data on a secure Newcastle University servers. No other directly identifiable data will be stored alongside the gait data.

Participants will be identified on REDCap via their unique trial ID number and DOB.

REDCap will also be utilised for its Alerts and Notifications features, to send alerts to remind participants to complete questionnaires (via email address and /or mobile number). Therefore, participant email address and mobile number will also be collected and stored on REDCap.

Participants will be fully informed of this and asked to consent as part of study consent, participants will also be able to opt-out of providing an email address or mobile number if preferred.

All efforts will be made to ensure that the data provided in the source documents is as complete as possible. Regular review of data completeness and regular data cleaning activities will be undertaken. These activities may include telephoning participants to obtain missing information.

Any activities which involve contacting study participants will be conducted by delegated members of the site team who are known to the participant (i.e. study research nurse).

REDCap

REDCap is an internet-based Electronic Case Report Form (eCRF) system.

The REDCap system utilised in this study will be provided by The Newcastle upon Tyne Hospitals NHS Foundation Trust. It is independently maintained and supported by Newcastle Hospitals. It is hosted on secure cloud servers held by AIMES. AIMES are an NHS certified cloud system provider based in Liverpool, UK.

The Newcastle Joint Research Office (NJRO) Research Informatics Team, manage and retain responsible for maintaining the local system, ensuring appropriate and secure access to the specific trial eCRF at a Sponsor/site level.

Management of the study's REDCap eCRF will be as per the relevant (NJRO) SOPs. Further information relating to REDCap and its security at Newcastle Hospitals is available via the NJRO website: https://newcastlejro.com/about/informatics/redcap/

Data Handling and Record Keeping

The study will comply with the General Data Protection Regulations (GDPR), 2018.

Data entry will be performed by a member of the research team at the site. Access to the study REDCap database will be restricted to research team members and associated REDCap administrators within Newcastle Hospitals only. Access to other study databases (i.e. gait database) will also be restricted to authorised team members only. Permission to access the study databases will be issued by the Chief Investigator.

Within the study databases, participants will be identified by a unique study ID number. Participant DOB, email address and mobile phone number (see above) may also be captured on the REDCap database however no other personal identifiers will be used.

The link between the participant's unique study ID number and their name will be via the study enrolment log (also known as the Participant Identification Log) which will be held in the ISF.

Pseudo-anonymised data, obtained as part of a separate study undertaken by Tubngen University, will be provided to the study team and combined with data from this study for analysis. This will include upload of some data items to the study REDCap database. All relevant data transfer agreements will be put in place prior to the transfer of such data.

Gait data from the Newcastle study will also be transferred to Tubingen for analyses. This will be pseudo-anonymised and will also be subject to the relevant data transfer agreements. The gait data transferred will not include any of the video recordings.

Newcastle Hospitals will provide data from REDCap to Newcastle University as Sponsor. Access to final datasets downloaded from REDCap and from the other study databases will be restricted to members of the study team and collaborators involved in data analyses. Such final datasets will be pseudo-anonymised and will not contain any direct personal identifiers.

The ISF will be held in a secure area at site with access restricted to the study team only. An electronic version of this log may also be held securely on NHS computer systems at site. The TMF will be held securely by the CI at the WCMR with access restricted to authorised team members and Sponsor representatives only.

Access to Data

Direct access to study data including source data contained in the participant's medical notes and elsewhere will be granted to authorised representatives of the Sponsor (Newcastle University), Newcastle Hospitals, or regulatory authorities for the purposes of monitoring, audit, or inspection. Consent for this will be obtained from participants during recruitment.

Following completion of the study, anonymised sets of raw data may be made available for 3rd party research purposes with the appropriate data transfer procedures.

Archiving

Archiving will be authorised by the Sponsor following submission of the end-of-study reports to REC and funder. Responsibility for archiving the ISF will sit with the study site and will be performed as per site SOPs. The TMF will be archived by Newcastle University according to the relevant University requirements.

Essential documents will be archived for a period defined by Sponsor. Destruction of essential documents following the required period of archiving will require sponsor authorisation.

De-identified (pseudo-anonymised) study data extracted from the study databases will be retained following the end of the study for further analysis. This data will be held securely on Newcastle University servers for up to 20 years.

Data collected and held on REDCap will be archived and destroyed at the direction of Sponsor and in accordance with the relevant NJRO SOPs for this.

Indemnity

Newcastle University has in place a Public Liability Policy which provides cover to the University for harm which comes about through the University's, or its staff's, negligence in relation to the design, management or conduct of the study. No arrangements for cover for non-negligent harm will be included.

Post-Study Care

Following the end of study, participants will undergo no further study assessments or procedures but will continue to receive routine clinical care from their direct care team.

Dissemination Policy

To communicate with academics and medical professionals, the intention will be to publish a number of scientific papers in peer-reviewed publications (open-access) and also to present lectures and posters at national and international academic conferences. The results will be used to curate a dataset repository and will be included in the AGI process to harmonize study protocols.

The study will be publicized on a number of partner and charity websites including AFAF, Ataxia Global Initiative (AGI), and Ataxia UK. Social media platforms may also be used to communicate research developments and to stimulate interest and communication amongst patient groups, academics, and the public.

At the end of the study and once results are available participants will be contacted directly by letter to thank them for their participation and to inform them of the study results. Any communications aimed at potential study participants and their families will be submitted for ethical review and approval before dissemination

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