Full Title:	EMERALD Pilot trial: **E**valuating the Tolerability and **E**fficacy of a **R**emote **M**icrophone (**A**ssisted **L**istening **D**evice) in Adults with Mitochondrial Disease
Short Title:	EMERALD
Protocol Version Number & Date:	Version 3.1, 04 December 2023
Sponsor:	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Sponsor Reference:	10224
Research Funder:	The Lily Foundation with support of My Mito Mission and in partnership with Phonak (A Sonova Company)

KEY PROTOCOL CONTRIBUTORS

Dr Renae J. Stefanetti
Research Associate & Honorary Physiologist
Wellcome Centre for Mitochondrial Research
Translational and Clinical Research Institute
Faculty of Medical Sciences
Newcastle University
Renae.stefanetti@ncl.ac.uk

Laura Brown
Senior Clinical Trials Manager
Wellcome Centre for Mitochondrial Research
Translational and Clinical Research Institute
Faculty of Medical Sciences
Newcastle University
laura.brown8@newcastle.ac.uk

SIGNATURES

Chief Investigator / Principal Investigator

Name: Professor Gráinne S. Gorman
Director of the Wellcome Centre for Mitochondrial Research & Honorary Consultant Neurologist
Wellcome Centre for Mitochondrial Research
Translational and Clinical Research Institute
Faculty of Medical Sciences
Newcastle University
grainne.gorman@ncl.ac.uk

Signature:

Date:

CO-INVESTIGATORS**Prof. Gary Rance**
Head of Department
Audiology and Speech Pathology
The University of Melbourne
grance@unimelb.edu.au

Prof. Lyndsay Pennington
Reader in Communication Disorders & Honorary Consultant Speech and Language Therapist
Population Health Sciences Institute
Faculty of Medical Sciences
Newcastle University
lindsay.pennington@ncl.ac.uk

Prof. Tim Griffiths
Professor of Cognitive Neurology
Henry Wellcome Building
Faculty of Medical Sciences
Newcastle University
tim.griffiths@newcastle.ac.uk

Dr Julien Zanin
Audiology and Speech Pathology
The University of Melbourne
julien.zanin@unimelb.edu.au
Hasan Colak
Auditory Cognition Lab
Faculty of Medical Sciences
Newcastle University
h.colak2@newcastle.ac.uk

ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
ALD	Assistive Listening Device
CI	Chief Investigator
CNC	Consonant-Nucleus-Consonant
CPIB	Communicative Participation Item Bank
CRF	Case Report Form
eCRF	electronic Case Report Form
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
ICF	Informed Consent Form
IOI-HA	International Outcomes Inventory Hearing
ISF	Investigator Site File
LIFE-H	Assessment of Life Habits
LiSN-S	Listening in Specialised Noise-Sentences
MFIS	Modified Fatigue Impact Scale
NHS	National Health Service
NMDAS	Newcastle Mitochondrial Disease Adult Scale
PA	Physical Activity
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
R&D	Research & Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SLA	Service Level Agreement
SOP	Standard Operating Procedure
SPaRQ	Social Participation Restrictions Questionnaire
SOS-HEAR	Significant Other Scale for Hearing Disability
SSQ	Speech, Spatial & Qualities of Hearing Scale
SUS	System Usability Scale
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
WCMR	Wellcome Centre for Mitochondrial Research
WHOQOL-BREF	World Health Organisation Quality of Life-BREF
QoL	Quality of Life

CONTENTS

TRIAL SUMMARY

Trial Title	EMERALD Pilot study: **E**valuating the Tolerability and **E**fficacy of a **R**emote **M**icrophone (**A**ssisted **L**istening **D**evice) in Adults Patients with Mitochondrial Disease
Short Title/Acronym	EMERALD
Summary of Design	Prospective, single centre, feasibility trial consisting of two phases: (1) Four-week, randomised, AB/BA crossover trial and (2) follow-on observational extension trial over 20 weeks (24 weeks in total). Participants will be randomly allocated (1:1 ratio) to one of two sequences: - Group 1: Aided with the device (2 weeks), followed by usual care (non-aided) (2 weeks); or - Group 2: Non-aided (2 weeks), followed by aided with the device (2 weeks).
Summary of Participant Population	Adults (16 to 70 years) with a proven genetic diagnosis of mitochondrial disease and reported mild to severe hearing loss. Partners/caregivers/close family members of included patients will also be involved, as we are interested in assessing the potential impact on caregiver burden.
Planned Sample Size	It is anticipated that N=24 patients with mitochondrial disease and reported hearing loss will need to be screened for N=12 eligible participants to be recruited to the trial (i.e., to meet the pre-specified eligibility criteria). This allows for trial completion by N=10 participants, allowing that approximately N=2 participants will withdraw.
Per Participant Duration	24 weeks
Proposed Overall Duration	12 months
Objective	Investigate the feasibility, tolerability and efficacy of a remote microphone assistive listening device (ALD) in adult participants with mitochondrial disease-related hearing loss.

BACKGROUND

Mitochondrial diseases are the most common group of genetic neurological disorders, affecting one in every 4,300 individuals in the UK and are a major problem for both patients and society because of the high level of suffering and associated disability[1]. Hearing loss and deafness both in isolation (non-syndromic) and as a feature of systemic mitochondrial disease (syndromic) is common, affecting between 50 - 80% of all cases at some time in the course of the disease[2-4].

Sound amplification by hearing aid remains the mainstay of symptomatic treatment. While hearing aids intensify sounds, unfortunately they do not enhance sound i.e., spoken word clarity.

Our pilot data suggest that impaired sound detection and/or auditory processing is the primary defect in mitochondrial disease-related hearing loss, limiting the effectiveness of hearing aids. Mitochondrial disease patients often report dissatisfaction or poor compliance, with the inability of a hearing aid to correct signal (sound) distortion with far-reaching implications on communication, psychological health, and quality of life (QoL).

Advances in technology have seen the rapid development of Assistive Listening Devices (ALDs) that can ameliorate communication and understanding difficulties for individuals with varying degrees of hearing loss and auditory processing deficits.

Novel remote microphone ALD systems, which can be used to enhance conventional hearing aids or can be stand-alone, employ wireless sound transmission to optimize the auditory signal by improving the signal-to-noise ratio for the user i.e., increasing the speaker's voice relative to background noise and thereby enhancing the user's ability to effectively understand speech.

Short term interventional studies (including by Rance et al. (Co-I)) have demonstrated the effects of ALDs in improving functional hearing in everyday listening situations[5, 6].

No trial has examined the tolerability and efficacy of what appears to be an innovative treatment strategy for mitochondrial disease-related hearing impairment.

TRIAL AIM

This pilot trial aims to explore the feasibility of the Phonak Roger On™ remote microphone, as an ALD in adults with mitochondrial disease hearing loss. This trial also aims to explore the far-reaching benefits to communication, social participation, and wellbeing, from ALD use.

OBJECTIVES & OUTCOME MEASURES

The **primary** trial objective is to:

- Evaluate the tolerability and usability of a remote microphone ALD in adults with mitochondrial disease hearing loss throughout the trial period of 24 weeks.

This will be assessed via:

- Investigator designed questionnaire of tolerability, acceptability and satisfaction.
- Validated questionnaires on usability and hearing aid satisfaction, if applicable, (System Usability Scale and International Outcomes Inventory Hearing), respectively.
- Compliance (participant reports of daily device use and setting of use).
- Device related adverse effects and undesirable effects (including technical issues).
- Participant withdrawal number and reason(s) for trial withdrawal.

The **Secondary** trial objective is to:

- Explore the efficacy of a remote microphone ALD in adults with mitochondrial disease hearing loss.

This will be measured by the following assessments* (results from Baseline will be compared with results from various points throughout the trial period):

- Consonant-Nucleus-Consonant (CNC) test
- Listening in Spatialised Noise-Sentences test (LiSN-S)
- Speech, Spatial and Qualities of Hearing Scale Short Form (SSQ-12) (participant self-rated)
- Communicative Participation Item Bank (CPIB) (participant self-rated)
- Significant Other Scale for Hearing Disability (SOS-HEAR) (caregiver rated)
- Assessment of Life Habits (LIFE-H- Short Form) (participant self-rated)
- Social Participation Restrictions Questionnaire (SPaRQ) (participant self-rated)
- World Health Organisation Quality of Life-BREF (WHOQOL-BREF) (participant self-rated)
- Modified Fatigue Impact Scale (MFIS) (participant self-rated)

* *Further details of the assessments are included in Table 1*

Table 1: Outcome Measures

Measure	Descriptors	Domain Assessed
CNC test	Phonemically balanced word list presented in 2 listening situations (quiet & with noise). Phonetically imitated; percentage of correct phonemes (speech sounds) calculated[5]	Speech perception
LiSN-S test	A Speech Reception Threshold is established in 4 conditions (vary in vocal differences & location to noise) to provide binaural assessment of speech perception (ability to segregate a target speech signal from background noise in a 3D-auditory environment)[7]	Spatial processing
Tolerability, Acceptability & Satisfaction (Appendix 1)	7-point Likert scale designed to investigating perceived usefulness, ease of use and behaviour intention	Tolerability, Acceptability & Satisfaction
Record of Adverse Events, Undesirable Effects &Technical Issues	Adverse Events, undesirable effects and technical issues will be reported by participants (to the trial team at all follow-ups and on an ad-hoc basis).	
SUS (Appendix 2)	10-item Likert originally designed to measure perceived ease-of-use of a device or system/technology; also provides usability (8-items) &learnability (2-items) subscales.	Usability
IOI-HA (Appendix 3)	7-item questionnaire designed to evaluate effectiveness of hearing aid treatments. This will be completed by participants who use hearing-aids.	Hearing-aid satisfaction
Compliance Diary	Participant reported daily diary of ALD use, including setting (e.g., meeting, transport, telephone) and their perceived experience of ALD use in real-time	Compliance
Number of participants who withdraw	The number of participants who are randomised but subsequently withdraw from the trial will be recorded. Reason/s for withdrawal and time-point details will be collected.	
NMDAS	Semi-quantitative, reproducible clinical rating scale of disease progression designed specifically for all forms of mitochondrial disease[8]	Disease burden
SSQ-12 (Short Version) (Appendix 4)	12-item version of full SSQ (a subjective assessment of listening and hearing ability in a variety of situations encountered in everyday life)[9]	Subjective hearing/ listening ability
CPIB (Appendix 5)	Verbal communication assessed in a range of interactions (46 items); validated and reliable PROMIS measure[10]	Communicative participation
SOS-HEAR* (Appendix 6)	A 36-item five-point scale developed to quantify 3rd party disability of hearing loss[11]	Caregiver burden
LIFE-H Short Form (Appendix 7)	Shortened version of LIFE-H which is a psychometrically robust tool to assess daily activities & social participation (life habits), based on self-perceived level of difficulty & assistance required.[12]T	Social participation
SPaRQ (Appendix 8)	19-item assessment of participation restrictions, comprising Social Behaviours and Social Perceptions due to hearing loss[13]	Participation restriction
WHOQOL-BREF (Appendix 9)	An international measure of QoL to evaluate overall perception of QoL and health[14]	Health-related QoL
Modified FIS (Appendix 10)	21-items; assessing the perceived impact of fatigue on cognitive, physical & psychosocial function. Modified version of the Fatigue Impact Scale[15]	Perceived fatigue impact

Abbreviations: IOI-HA, International Outcomes Inventory Hearing; SUS, Systems Usability Scale.
**completed by partners/caregivers/close family members (non-mandatory). Participants will still be eligible they do not have a partners/caregivers/close family member who is able or willing to participate*.

TRIAL DESIGN AND SETTING

This single-centre, prospective pilot trial will take place in tertiary care within the Newcastle upon Tyne NHS Hospitals Foundation Trust (Newcastle Hospitals). Wherever possible, participants will have their End of Trial visit coincide with their routine clinical visit to the Newcastle Mitochondrial Disease Clinic for Adults and Children.

Trial visits will also take place at the Newcastle University Medical School (Auditory Cognition Group) https://www.auditorycognition.org/ (Screening/Baseline only) and NE1Hear https://www.ne1hear.co.uk/, where participants will undergo auditory assessment and ALD device fitting by qualified audiologists. NE1Hear have been contracted by Newcastle Hospitals to provide NHS services and will provide hearing assessments for this trial as per a relevant SLA.

Data will be captured at site, at Newcastle University and by NE1Hear, and will also be captured remotely (i.e., participant questionnaires completed at home, or experience data completed in real-time in any setting). Data will be collated via the REDCAP electronic Case Report Form (eCRF) system.

This trial will consist of two phases:

1) **Four-week randomised, AB/BA crossover trial**

   Participants will be randomly allocated (1:1 ratio) to one of two sequences:

   - Group 1: ALD-Aided (2 weeks), followed by usual care (non-ALD-Aided) (2 weeks); or
   - Group 2: Non-ALD-Aided (2 weeks), followed by ALD-Aided (2 weeks)

2) **Follow-on observational trial extension over 20 weeks**

   All participants will use the ALD for a period of 20 weeks following the end of the crossover period.

This means that the trial duration per participant will be 24 weeks in total.

It is anticipated that a minimum of 24 patients with mitochondrial disease and self-reported hearing loss will be screened in order to recruit 12 eligible participants (based on our previous findings as well as published studies reporting hearing loss and auditory processing deficits in patients with mitochondrial disease). Accounting for ~10% attrition (if two participants withdraw from the trial), this will allow for the trial to be completed by ten participants.

In total, participants will attend for four visits:

- Screening / Baseline, to be completed on the same day (at both Newcastle University and NE1Hear)
- Week 2 (NE1Hear)
- Week 4 (NE1Hear)
- Week 24 (NE1Hear and Newcastle Hospitals)

TRIAL DEVICE

The device being utilised in this trial is the Phonak Roger On™ remote microphone. The Roger On™ is developed and manufactured by Phonak (a Sonova Company) https://www.phonak.com/uk/en/about-us.html.

Phonak have agreed to donate the devices to the Wellcome Centre for Mitochondrial Research, Newcastle University. The devices will be provided to participants for the duration of the trial.

This trial will be classed as a non-commercial trial of a UKCA/CE UKNI/CE marked device for a labelled indication, involving a change to standard care or randomisation between groups.

As it is taking place at a single site in England, MHRA notification of no objection is not required.

ELIGIBILITY CRITERIA

Eligibility must be assessed by a suitably qualified and delegated member of the trial team (either a medically qualified doctor or appropriately experienced research team member e.g., research nurse, physiotherapist, exercise physiologist), and this assessment documented in the participant's medical records.

Only personnel formally delegated by the PI may assess eligibility.

Inclusion Criteria

To be eligible to participate all participants must:

- Be between 16 years and 70 years (aged ≥16 to ≤ 70 years)
- Have ability, in the opinion of the trial team, to participate in trial activities
- Be capable of providing informed consent
- Have a genetically confirmed diagnosis of mitochondrial disease
- Have confirmed hearing loss- via NMDAS hearing score of: 2 (mild), 3 (moderate), or 4 (severe)
- Have an NMDAS speech score of: 0 (normal), 1 (communication unaffected), or 2 (mild communication difficulties).
- Have evidence of impaired speech perception in background noise due to:
    - Significant sound detection defect measured by a 4-frequency average hearing detection threshold level (pure-tone-audiometry, ≥60 dBHL in the poorer ear) and/or
    - Impaired auditory processing (≤2 SDs from the normative mean) assessed by the 'Speech Reception Threshold' subtest of the Listening in Specialised Noise-Sentences (LiSN-S) test most reflective of everyday listening
- If hearing aid users: Use Phonak hearing aids that are compatible with the remote microphone ALD and be willing to continue using hearing aid(s) during the trial.
- If non-hearing aid users: Be willing and able to use a receiver device e.g., 'Roger Focus' which will be paired to the ALD during the device use periods of the trial. This receiver will be provided by the trial alongside the ALD.

Partners/caregivers/close family members of participants will be asked to complete a caregiver burden questionnaire (SOS-Hear) as part of the trial (non-mandatory). If their participation is declined, a participant's ability to take part will not be affected.

Exclusion criteria

Participants will not be eligible if they:

- Have an NMDAS hearing score of 0 or 1 - no communication problems; tinnitus or deterioration from prior 'normal'
- Have an NMDAS speech score of 3 (moderate difficulties) or above
- Have profound/end stage hearing loss i.e. NMDAS hearing score of 5
- Have conductive hearing loss (≥10-dB air-bone gap at 500 - 3000 Hz)
- Have current local ear intolerances or issues preventing hearing aid/ALD effectiveness or use i.e., ear infection, significant earwax
- Are currently using, or have previously used, a Roger On remote microphone assistive listening device
- If hearing aid users:
    - Use of non-compatible hearing aids (non-Phonak)
    - Planning a change to their hearing aid(s) during the course of the trial
- Any other medical issues, which in the opinion of the investigator would preclude involvement.

Note on Participant Genotypes Mitochondrial disease hearing loss is commonly associated with the m.3243A>G pathogenic variant. In order to ensure that this genotype is adequately represented within the study population, a minimum of 50% of participants should be recruited who have the m.3243A>G genotype. A log of participant genotypes will be maintained and the numbers of relevant genotypes monitored. Once a total of six participants with other genotypes have been recruited, recruitment will be restricted to participants with m.3243A>G only.

RECRUITMENT AND CONSENT

Participant identification

Patients will be identified for the trial by their direct clinical care team at the Newcastle Mitochondrial Disease Clinic for Adults and Children. This will be via screening of clinic

lists and by interrogation of the Wellcome Centre for Mitochondrial Research Patient Cohort: A Natural History Study and Patient Registry (MitoCohort) (previously known as the MRC Mitochondrial Disease Cohort), REC Ref: 13/NE/0326.

The MitoCohort, which is a natural history study and patient registry, has > 1900 registered patients with extensive storage of clinical and genetic information. Patients registered on the MitoCohort have consented to receive information about clinical trials and studies for which they may be eligible.
The MitoCohort database will be interrogated for adult patients registered at the Newcastle site with a genetically confirmed diagnosis of mitochondrial disease and mild to severe hearing loss (NMDAS hearing subscale score: 2 to 4).

In addition to recruitment from the MitoCohort, patients seen by the Mitochondrial Clinical Service in Newcastle (at the Newcastle Mitochondrial Disease Clinic for Adults and Children), who are identified by their direct care team as being potentially eligible for the trial, may also be approached.

The trial will also be publicised on a number of websites including the website of mitochondrial disease charities and partner organisations (i.e. the Lily Foundation) and promoted at public and patient engagement events and conferences. Any website or trial advertisement will advise patients who are interested to contact the trial team for further information and a clinical referral to the trial team in Newcastle will be requested.

Potentially eligible patients will be sent an invitation letter along with a copy of the relevant Participant Information Sheet (PIS), or will be contacted (via telephone, email or in person) by their direct clinical care team and invited to participate.

A trial invitation/pre-screening log will be kept which will include details of all individuals who are invited to participate in the trial/are pre-screened for trial participation. This log will include the reason for declining the invitation or pre-screen failure (if applicable/provided).

Informed Consent

Written informed consent will be obtained from all participants prior to the start of screening assessments. This will be obtained by appropriately qualified, experienced and delegated members of the research team at site.

Consent will be received by means of initialling to confirm agreement of each consent statement followed by participant dated signature and dated signature of the person who received the informed consent.
A copy of the signed Informed Consent Form will be given to the participant and a copy filed in their hospital records. The original signed Consent Form will be stored in the Investigator Site File (ISF).

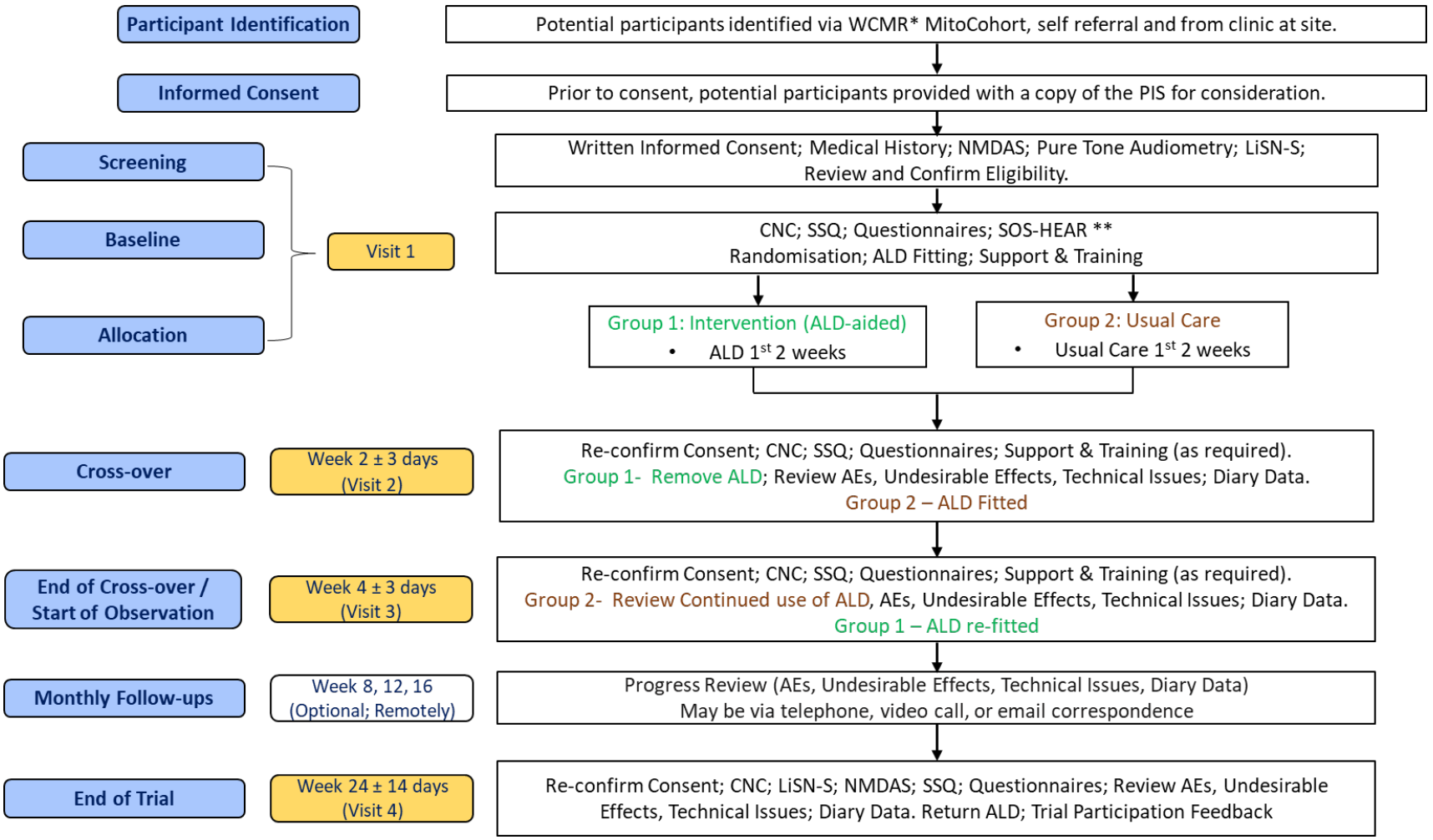
A letter will be sent to the participant's general practitioner to inform them of their patient's participation in this trial. A copy of this letter will be filed in the participant's hospital records.

A caregiver, close family member, or partner, of each participant will be asked to complete a Caregiver Burden Questionnaire (SOS Hear) – this will be optional and a participant will still be able to take part without this. Completion of the questionnaire by the caregiver/family member/partner will be taken as their consent to be involved. Separate written consent will not be obtained.

No identifiable information about the caregiver or family member who completes the questionnaire will be used in the analyses.

Email address and/or mobile phone number of participating caregivers/family members will be collected and stored on REDCAP in order to send out links to online questionnaires (if applicable).

TRIAL PROCEDURES



Screening / Confirmation of Eligibility

Formal screening activities will be undertaken once the participant has provided consent. In advance of this, the research team will review the medical history of potential participants to confirm that it is worth proceeding with formal screening activities.

A screening log, which will include details of all participants who are formally screened will be retained. This log will include the reason for any screen failures (if applicable).

The following assessments/activities will be conducted at the screening visit at Newcastle University:

- **Written Informed Consent**
- **Collection of Medical History, medication details and demographics** (to include age, sex, ethnicity, genetic diagnosis, alcohol consumption, smoking status, socio-economic status i.e. postcode and employment, activities of daily living)
- **Newcastle Mitochondrial Disease Adult Scale (NMDAS)***
- **Atkin & Fisher's Articulation Survey***
- **Pure-tone-audiometry** (*eligibility assessment)*
- **Speech-in-noise (SiN) tests**

*If an NMDAS has been performed within 6 months prior to the visit, the results from the existing NMDAS can be used and there will be no requirement to perform this assessment at the visit.

The following assessments/activities will be conducted at the screening visit at NE1Hear (see Table 1):

- **LiSN-S test** (*eligibility assessment)*
- **Eligibility Confirmation**

Baseline Visit (Week 0)

It is anticipated that, once eligibility has been confirmed, participants will proceed directly to Baseline (on the same day). However, this is not mandatory. In all circumstances, Baseline should take place within 14 days of confirmation of eligibility.

Baseline Assessments/Activities will consist of:

- **Verbal Re-confirmation of Consent** (agreement to continue participation).
- **Fitting of ALD**
- **CNC test*** (completed in two conditions –ALD-Aided & non-ALD-Aided; test order will be randomly allocated to participants)
- **Participant completed questionnaires:** SSQ-12, MFIS, CPIB, SPaRQ, LIFE-H (Short Form), WHOQOL-BREF, IOI-HA (if applicable)
- **Caregiver completed questionnaire (if applicable):** SOS-HEAR.
- **Clinical review of medical notes and collection of existing medical information and previous results.** Including:
  - Neuroimaging (e.g., MRI)
  - Neurophysiology (e.g., Nerve conduction studies, electromyography, EEG)
  - Cognitive tests
  - Laboratory tests
  - Genetic tests and mtDNA heteroplasmy levels (results from any tissues)
  - Other relevant assessments (e.g., audiology, brainstem evoked potential).

Randomisation and Device Fitting

Following completion of Baseline activities, participants will be randomly assigned to one of two groups, to begin the four-week crossover trial:

- Group 1 (ALD-Aided): Start with the device for the first two weeks; followed by usual care for the following two weeks. Allocated participants will have the device appropriately fitted for immediate use upon leaving site (for two weeks).
- Group 2 (Usual Care): Allocated to usual care for the first two weeks before starting with the device for the following two weeks. Although the participants allocated to Group 2 will have the remote microphone ALD appropriately fitted at Baseline (e.g., to ensure compatibility with current hearing aids if required and to perform part of the CNC Baseline test), they will not leave the site with the device until after the two-week (usual care) period.

Support and Training

Participants and caregivers will be provided with training resources on how to use their remote microphone ALD in a range of situations and how to access support if required. In addition to support and training on ALD use by the research team, participants/carers will be provided with a helpline number and access to video support on ALD use from the manufacturer (Phonak, a Sonova Company).

Participants will also be instructed on how to complete their diary of ALD use and completion of the other questionnaires remotely using the REDCAP ePRO system.

Week 2 Visit (Crossover)

The Week 2 visit will take place at the trial site 14 days (+/- 3 days) following Baseline. **Week 2 Assessments/Activities** will consist of:

- **Verbal Re-confirmation of Consent** (agreement to continue participation).
- **CNC test*** (completed in two conditions –ALD-Aided & non-ALD-Aided; test order to be the same as at Baseline)
- **Participant completed questionnaires:** SSQ-12, Tolerability Acceptability and Satisfaction*, and SUS*, IOI-HA (all applicable participants i.e., hearing-aid users)
- **Review of any Adverse Events, Undesirable Effects and Technical Issues***
- **Review of Diary Data (compliance)***
- **Support and Training** as required

* *If applicable- ALD-Aided group only*

Device Removal/ Re-Fit for Use

Following completion of the first two-week period, participants will 'crossover' treatment groups for the second two-week period to complete the crossover trial:

- Group 1 (ALD-Aided): Participants will return the device to site and undergo two weeks of usual care.
- Group 2 (Usual Care): Participants will have the device appropriately fitted at site- for two weeks of use.

Week 4 (End of Crossover / Start of Trial Extension Phase)

The Week 4 visit will take place at the trial site 14 days (+/- 3 days) following the Week 2 visit.

Week 4 Assessments/Activities will consist of:

- **Verbal Re-confirmation of Consent** (agreement to continue participation).
- **CNC test*** (completed in two conditions– ALD-Aided & non ALD-Aided; test order to be the same as at Baseline)
- **Participant completed questionnaires:** SSQ-12, Tolerability Acceptability and Satisfaction*, and SUS*, IOI-HA (all applicable participants i.e., hearing aid users)
- **Review of any Adverse Events, Undesirable Effects and Technical Issues***
- **Review of Diary Data (compliance)***
- **Support and Training** as required

* *If applicable- ALD-Aided group only*

Device Re-Fit for Use – for the Trial Extension

Following completion of the crossover trial:

- Group 1 (ALD-Aided): Participants will have the device appropriately re-fitted at site for a further 20 weeks of use.
- Group 2 (Usual Care): Participants will return to site, where they will be reviewed for continued use of the device (if required) for a further 20 weeks.

Weeks 8, 12 & 16 Monthly Follow-ups (Optional)

Participants will be offered monthly follow-ups with the trial team (remotely) to check on progress and report on any issues experienced. Follow-ups may be via telephone, video call, or email correspondence (depending upon participant preference). Monthly follow-ups are optional and will be based on participant preference. Participants will also be free to contact the trial team on an ad-hoc basis if they have any questions or issues to report.

Week 24

The Week 24 visit will take place at the trial site 20 Weeks (140 days) (+/- 14 days) following the Week 4 visit.

Week 24 Assessments/Activities will consist of:

- **Verbal Re-confirmation of Consent** (agreement to continue participation).
- **Collection of updated medical history, medications and demographics**
- **LiSN-S test**
- **CNC test*** (completed in two conditions –ALD-aided & non-ALD aided; test order to be the same as at Baseline)
- **Participant completed questionnaires**: Tolerability Acceptability and Satisfaction, SUS, IOI-HA (if applicable), SSQ-12, MFIS, CPIB, SPaRQ, LIFE-H (Short Form), WHOQOL-BREF
- **Caregiver completed questionnaire (if applicable):** SOS-HEAR
- **Newcastle Mitochondrial Disease Adult Scale (NMDAS)**
- **Clinical review of medical notes and collection of updated existing medical information and previous results** (see Baseline visit for details)
- **Review of any Adverse Events, Undesirable Effects and Technical Issues**
- **Review of Diary Data (compliance)**
- **Feedback on trial participation.** The participant will be asked to provide feedback on their experience of the trial. This will be optional and participants do not need provide feedback if they do not wish to do so.

Device Removal

Following completion of the End of Trial visit:

- All participants will return their devices and return to usual care.

<u>* Note on Atkin & Fisher's articulation survey and CNC tests</u>

These assessments will be audio recorded and the recordings stored so that scores can be checked and, if applicable, verified by independent assessors during the analyses stage. Audio recordings will be de-identified for storage and analyses purposes (utilising unique participant ID only). Consent will be obtained from participants to use these audio recordings in future research.

End of Study

The End of Study for each participant will be completion of the required assessments and activities at Week 24 (Visit 4) and returning the device. The overall end of study will be defined as completion of data collection, data cleaning and data analyses.

Withdrawal Visit (if required)

Participants who withdraw, or are withdrawn, from the trial at any point following randomisation will be invited to attend a withdrawal visit.

At this visit the following assessments/activities will take place:

- **Return of the ALD** (if applicable- if a participant withdraws during the non-ALD-Aided phase of the crossover there will be no ALD to return and the withdrawal visit may be completed remotely).
- **Review of reason for withdrawal.**
- **Review of any Adverse Events, Undesirable Effects and Technical Issues**
- **Review of Diary Data (compliance)**
- **Feedback on trial participation.** The participant will be asked to provide feedback on their experience of the trial. This will be optional and participants do not need provide feedback if they do not wish to do so.
- ***If appropriate,*** participants will be asked to re-complete follow-up trial questionnaires (optional).

SCHEDULE OF EVENTS

Trial Assessments	Visit 1 (Trial site)			Visit 2 (Site)	Visit 3 (Site)	Follow up (Remote)	Visit 4 (Site)	Withdrawal Visit (Site)
	Screening		Baseline	Crossover	End of crossover/ Start of observation	Observation	End of Trial	As applicable
	Newcastle University	Ne1Hear						
	Week 0			Week 2 +/- 3 days	Week 4 +/- 3 days	Monthly +/- 7 days	Week 24 +/- 14 days	
Informed Consent	X							
Medical History	X						X	
Medication Review	X						X	
NMDAS (or collection of results from existing NMDAS)	X						X	
Demographics	X						X	
Atkin & Fisher's Articulation Survey	X							
Speech-in-noise (SiN) tests	X							
Pure-tone-Audiometry	X							
LiSN-S Test		X					X	
Eligibility Confirmation		X						
Re-confirm Consent			X	X	X	X	X	
Assistive Listening Device (ALD) Fitted			X (1)	X (2)	X (1 & 2)			
CNC Test *			X	X	X		X	
Speech, Spatial & Qualities of Hearing Scale (SSQ-12)			X	X	X		X	X (†)
MFIS, CPIB, SPaRQ, LIFE-H (Short Form), WHOQOL-BREF, & SOS-HEAR ‡			X				X	X (†)
Randomisation			X					
Tolerability Acceptability & Satisfaction Questionnaire, SUS, IOI-HA‡				X	X		X	X (†)
Review of any Adverse Events, Undesirable Effects & Technical Issues				X	X	X	X	X
Review of Diary Data (compliance)				X	X	X	X	X
Clinical review of medical notes/collect relevant clinical information			X				X	
Technical Support (from research team and Phonak/Sonova)			X	X	X	X	X	
Return ALD							X	X
Participant Feedback (optional)							X	X

* Completed in 2 conditions (ALD-Aided and non-ALD-Aided); test order randomly allocated to participants at Baseline and the same order repeated at each visit

(1) Group 1: ALD-Aided for the first 2 weeks (will have tolerability, usability and satisfaction reviewed at Week 2 visit and will record AEs and compliance for first 2 weeks)

(2) Group 2: Usual care (non-ALD-Aided) for the first 2 weeks (will have tolerability, usability and satisfaction reviewed at Week 4 visit and will record AEs and compliance from weeks 2-4)

(1 & 2) Group 2 who used the ALD in the preceding 2 weeks will continue to use the device, Group 1 will have the device re-fitted and commence use again

‡Note on Questionnaires: After Baseline, participants will be able to complete their questionnaires via REDCAP. Relevant questionnaires will be enabled in REDCAP for completion for three days prior to the trial visit. Checks will be undertaken at the visit to ensure completion and completion on paper offered during the visit if needed.

(†) If appropriate, participants will be asked to re-complete follow-up trial questionnaires upon withdraw (optional).

Withdrawal Criteria

Participants have the right to withdraw from the trial at any time without having to give a reason. Participants who choose to withdraw from the trial will be advised that the data collected up to the point of their withdrawal will be retained.

A member of the research team should try to ascertain the reason for withdrawal and document this reason within the participant's medical notes (see withdrawal visit information for further details).

The Investigator may discontinue a participant from the trial at any time if the Investigator considers it necessary for any reason including:

- Participant withdrawal of consent
- Participant loss of capacity to provide informed consent
- 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 trial
- Termination of the trial by the sponsor or funder

If participants are withdrawn from the trial, the information already obtained will be kept. Participants will be advised of this during recruitment and consent.

End of Trial

The end of trial for each participant will be completion of their End of Trial visit (Week 24).

RANDOMISATION AND DATA COLLECTION

Randomisation for the crossover period of the trial will be managed through REDCAP, a browser-based Electronic Case Report Form (eCRF) system (https://projectredcap.org/about/). Trial data will also be collated via the REDCAP eCRF, including entry of participant reported outcomes directly onto the system (ePROs).

Randomisation

A customised allocation list for participant allocation will be created (with provision of examples) and provided to the RECAP team for upload. Participants will be randomised in a 1:1 ratio, using variable length random permuted blocks (of size 2 and 4) in R statistical software by the trial statistician.

Data Management

Data Collection Tools and Source Documentation Identification

Completed trial consent forms will be held in the combined TMF/ISF. Copies will be held in the participant medical records.

Source data for this trial will consist of annotations in the participant medical records, trial specific researcher assessment tools and worksheets, participant completed questionnaires and diaries (including ePROs recorded via REDCAP),audiology reports issued by NE1Hear and audio recordings of the Atkin & Fisher's Articulation Survey and CNC tests.

Additionally, participants will be required to complete hearing assessments via the relevant software on Newcastle University laptops and computers. Access to the computers will be restricted to authorised members of the study team and will be protected via password.

The tests will be administered to participants by a member of the research team who will be present throughout. The software used does not require identifiable details, therefore participants will not be required to provide their name or enter any identifiable details when undertaking the tests. All participants will be identified on the relevant software via their unique study participant ID.

Where participants remotely enter outcomes directly through REDCAP, they will be sent a reminder link by telephone and/or email to complete self-reported questionnaires. To ensure inclusivity, if participants are unable to utilise the online system, the trial team will work with them to enable completion of data over the telephone, face-to-face, or paper based questionnaires via post.

Completed researcher/clinician assessment tools will be stored in the TMF/ISF. Participants will be identified on any assessment tools via their unique trial ID number rather than by name.

Reports issued by NE1Hear (in the form of PDF documents forwarded to the trial team by secure nhs.net email) will also identify participants by their unique trial ID number. These will be printed on receipt at site and added to the TMF/ISF. Copies will also be added to the participants' hospital records.

Audio recordings of the Atkin and Fisher's Articulation Survey and CNC test will be captured using a digital recording device. Recordings will then be downloaded onto a secure Newcastle University shared drive folder for storage. Once stored, the original recordings will be deleted from the device. Recordings will be pseudo-anonymised and will identify participants by their unique study ID only.

To arrange trial visits, the study team will email (or phone) NE1Hear. The personal identifiable information required to arrange visits (consisting of participant name and screening ID) will be communicated via email, secure internal post, or phone.

Data will be transcribed from the source data directly onto REDCAP (with the exception of the ePRO where RECAP will be the source data). Participants will be identified on REDCAP via their unique trial ID number and DOB (i.e., the trial database will be classed as containing pseudo-anonymised data only). 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).

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 trial participants will be conducted by delegated members of the site team who are known to the participant (i.e., trial research nurse).

REDCAP

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

The REDCAP system utilised by The Newcastle upon Tyne Hospitals NHS Foundation Trust (which will be used in this trial) 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 trial's REDCAP eCRF will be as per the relevant Sponsor (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 trial will comply with all relevant data protection legislation.

Data entry will be performed by a member of the research team at site. Permission to access the trial database will be issued by the Chief Investigator.

Within the trial database, participants will be identified by a unique trial ID number and DOB. Their contact email address and mobile number (and the contact email address of their caregiver if applicable) will also be captured and recorded on the system for the purpose of allowing ePRO entry and issuing alerts; no other personal identifiable information will be used.

The link between the participant unique trial ID number and their name will be via the trial recruitment log which will be held in the TMF/IS (held in a secure area at site, with access restricted to the research team only). An electronic version of this log may also be held securely on NHS computer systems at site.

Identifiable data (including information contained in audiology reports) will be transferred between Newcastle Hospitals and NE1Hear via phone, secure email (nhs.net to nhs.net) and secure internal post.

Following completion of the trial, pseudo-anonymised sets of raw data (including audio recordings) may be made available for 3rd party research purposes with the appropriate data transfer procedures.

The data will also be made available as open research data. Consent for this will be obtained from all participants.

Access to Data

Direct access to trial data including source data contained in the participant medical notes and personal identifiable data contained in the TMF/ISF will be granted to authorised representatives of the Sponsor, or regulatory authorities for the purposes of monitoring, audit or inspection. Consent for this will be obtained from participants during recruitment.

Archiving

Archiving will be authorised by the trial Sponsor following submission of the end of trial reports to REC and funder. As the sponsor and site are within the same NHS organisation, all trial essential documents from a site and Sponsor perspective will be archived together.

Essential documents will be archived for a period defined by Sponsor and archiving will be according to Sponsor processes and procedures. Destruction of essential documents following the required period of archiving will require Sponsor authorisation.

Archiving of source documents generated and held by NE1Hear will be as per NE1Hear polices and processes.

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

STATISTICS

Compliance, tolerability, satisfaction, experience and withdrawal data will primarily be summarised using descriptive statistics and/or visually.

Where appropriate, suitable mixed models may be used to explore longitudinal effects on these data (e.g., temporal within subject changes in compliance). The analysis of the secondary trial objectives efficacy outcome data) will be considered exploratory given the trial sample size.

MONITORING, AUDIT & INSPECTION

The trial may be subject to audit or monitoring by representatives of the Sponsor and Newcastle University, or inspection by regulatory authorities.

Each investigator will permit trial-related monitoring, audits and regulatory inspection including access to all essential and source data relating to the trial. The site research team will follow local standard regulatory and quality assurance practices.

ADVERSE EVENT & ADVERSE INCIDENT REPORTING

Adverse Events and Serious Adverse Events

Due to the nature and purpose of the trial, only adverse events relating to the following will be reported for each participant:

- Hearing and ear health (including any ear infections)
- Hearing-aid use (where applicable)
- ALD use
- Events occurring during, or as a direct result of, trial visits/assessments.

Such adverse events will be documented in the participant medical notes recording causality and severity. They will also be recorded on the trial adverse event log. AEs will be followed up until resolution or until stabilisation (if complete resolution is not anticipated).

A Serious Adverse Event (SAE) for this trial will be defined as an adverse event (as requiring reporting above), which occurs and also meets 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.*

In the event of a SAE, the Sponsor, The Newcastle upon Tyne Hospitals NHS Foundation Trust, will be notified immediately by email (within 24 hours of site awareness of the event) and the following details provided:

- Participants Unique Trial 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 trial participation or trial procedures) - This needs to be confirmed by the PI or delegated investigator who is medically qualified.
- Expectedness (if related to a trial procedure whether this is an 'expected' event)- This also needs to be confirmed by the PI or a delegated investigator who is medically qualified
- Action Taken
- Outcome/Current Status
- Resolution Date (if applicable)

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 Sponsor as required until resolution.

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

Any SAEs that are related to a trial assessment/visit and that are classified as unexpected will be reported to the Research Ethics Committee by Sponsor and also reported to other Sponsor departments as per Sponsor procedures.

Adverse Incidents (ALD issues)

Any technical or other issues experienced by participants relating to operation and functionality of the ALD will be reported. This will include any incidences of loss or damage to the device. These will be recorded as Adverse Incidents and recorded in a trial-specific Adverse Incident Log. Details of the issue incident including what assistance was required and whether resolution of the incident was possible will be recorded.

Abnormal Results or Issues of Concern

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

ETHICAL AND REGULATORY CONSIDERATIONS

Regulatory Compliance and Research Ethics Committee Review and Reports

The trial will be conducted in accordance with sponsor 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 trial. All parties will conduct the trial in accordance with this ethical opinion.

The CI will notify the REC of all required substantial amendments to the trial. Substantial amendments that require a REC favourable opinion will not be implemented until this REC favourable opinion is obtained. The Sponsor will notify the REC of any serious breaches of GCP or the protocol that occur during the trial.

An annual progress report will be submitted each year to the REC by the CI until the end of the trial. This report will be submitted within 30 days of the anniversary date on which the original favourable ethical opinion was granted.

The CI will notify the REC of the early termination or end of trial in accordance with the required timelines.

Deviations

The Chief Investigator will be responsible for ensuring the trial is conducted according to the protocol and GCP.

Protocol deviations, non-compliances and breaches are departures from the approved protocol. Any deviations from the protocol and GCP should be documented on the trial deviation log. This log will be reviewed by the PI on a regular basis. Where necessary, Corrective and Preventative Actions (CAPA) will be implemented. These will also be documented and reported to the CI and Sponsor.

If the deviation constitutes a violation, this must be recorded on the log and reported to CI and Sponsor in a timely manner (within 3 working days).

Deviations found to frequently recur at a site are not acceptable and could be classified as a serious breach.

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 trial; or
b) the scientific value of the trial

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 sponsor SOP.

Indemnity

The Newcastle Upon Tyne Hospitals NHS Foundation Trust has liability for clinical negligence. NHS Indemnity covers NHS staff and medical academic staff with honorary contracts for potential liability in respect of negligent harm arising from the conduct of the trial.

As Sponsor, the Newcastle upon Tyne Hospitals NHS Foundation Trust will provide indemnity in respect of potential liability and negligent harm arising from trial management.

Indemnity in respect of potential liability arising from negligent harm related to trial design is provided by Newcastle University.

This is a non-commercial trial and therefore there are no arrangements for non-negligent compensation.

Amendments

It is the responsibility of the Research Sponsor to determine if an amendment is substantial or not and trial 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 authorisation is received.

Post-Trial Care

Following the trial, participants will not have any further trial assessments or procedures, but will continue to receive standard care from their clinical care team.

Unfortunately, due to the fact that this a pilot trial, it will not be possible for participants to keep the ALD following trial completion. The ALDs will be returned to the research team and will be utilised in future research. Participants will be fully informed of this at the outset.

COMMUNICATION AND DISSEMINATION OF RESULTS

Findings from the trial may be reported at local, national and international meetings, on social media platforms (including but not limited to, Newcastle University, Wellcome Centre for Mitochondrial Research, charity partners), as well as in peer-reviewed journals.

Trial participants will be advised in the Participant Information Sheet that they can contact the research team to request a lay summary of the overall research results once the trial is complete.

CONTACT FOR FUTURE RESEARCH, PPI AND ENGAGEMENT ACTIVITIES

Participants who agreed to take part in the trial, including those who fail screening, will be invited to provide their contact details to Newcastle University so that they can be contacted for the following purposes:

- To inform them about future research opportunities in mitochondrial disease and hearing, including invitations to take part in future research.
- To invite them to take part in Patient and Public Involvement (PPI) activities relating to mitochondrial disease and clinical research.
- To notify them about engagement activities and initiatives being run by the Wellcome Centre for Mitochondrial Research and Newcastle University and to invite them to take part in these.

This will be optional, participants will be able to take part in the trial without agreeing to the collection and storage of their data for this purpose. The purpose for collecting and storing this information and its legal basis (which is separate to the research) will be clearly explained to participants. Explicit consent for this processing purpose will be obtained.

Newcastle University will retain the contact details collected for this purpose securely within the WCMR in accordance with GDPR and all applicable UK legislation. Participants will be able to request that these details are updated and erased at any point.

REFERENCES

1. Gorman GS, Schaefer AM, Ng Y, et al. Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. Ann Neurol 2015;77:753-759.
2. Kullar PJ, Quail J, Lindsey P, et al. Both mitochondrial DNA and mitonuclear gene mutations cause hearing loss through cochlear dysfunction. Brain 2016;139:e33.
3. Edmonds JL, Kirse DJ, Kearns D, Deutsch R, Spruijt L, Naviaux RK. The otolaryngological manifestations of mitochondrial disease and the risk of neurodegeneration with infection. Arch Otolaryngol Head Neck Surg 2002;128:355-362.
4. Chinnery PF, Bindoff LA. 116th ENMC international workshop: The treatment of mitochondrial disorders, 14th-16th March 2003, Naarden, The Netherlands. Neuromuscular Disorders 2003;13:757-764.
5. Rance G, Corben LA, Du Bourg E, King A, Delatycki MB. Successful treatment of auditory perceptual disorder in individuals with Friedreich ataxia. Neuroscience 2010;171:552-555.
6. Rance G, Saunders K, Carew P, Johansson M, Tan J. The Use of Listening Devices to Ameliorate Auditory Deficit in Children with Autism. J Pediatr-Us 2014;164:352-357.
7. Cameron S, Dillon H. Development of the Listening in Spatialized Noise-Sentences Test (LISN-S). Ear Hear 2007;28:196-211.
8. Schaefer AM, Phoenix C, Elson JL, McFarland R, Chinnery PF, Turnbull DM. Mitochondrial disease in adults: a scale to monitor progression and treatment. Neurology 2006;66:1932-1934.
9. Noble W, Jensen NS, Naylor G, Bhullar N, Akeroyd MA. A short form of the Speech, Spatial and Qualities of Hearing scale suitable for clinical use: the SSQ12. Int J Audiol. 2013 Jun;52(6):409-12. doi: 10.3109/14992027.2013.781278. PMID: 23651462; PMCID: PMC3864780.
10. Baylor C, Yorkston K, Eadie T, Kim J, Chung H, Amtmann D. The Communicative Participation Item Bank (CPIB): item bank calibration and development of a disorder-generic short form. J Speech Lang Hear Res 2013;56:1190-1208.
11. Scarinci N, Worrall L, Hickson L. The effect of hearing impairment in older people on the spouse: development and psychometric testing of the significant other scale for hearing disability (SOS-HEAR). Int J Audiol 2009;48:671-683.
12. Noreau L, Fougeyrollas P, Vincent C. The LIFE-H: Assessment of the quality of social participation. Technology and Disability 2002;14:113-118.
13. Heffernan E, Maidment DW, Barry JG, Ferguson MA. Refinement and Validation of the Social Participation Restrictions Questionnaire: An Application of Rasch Analysis and Traditional Psychometric Analysis Techniques. Ear Hear 2019;40:328-339.
14. Billington R. WHOQOL annotated bibliography: October 1999 version. In: Geneva S, ed. World Health Organization, Department of Mental Health1999.
15. Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schlech WF. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. Clin Infect Dis 1994;18 Suppl 1:S79-83.