ClinicalTrials.gov Identifier: NCT04200664

FULL/LONG TITLE OF THE STUDY

CLINICAL AND IMAGING BIOMARKERS OF AUDIOVESTIBULAR FUNCTION IN INFRATENTORIAL SUPERFICIAL SIDEROSIS
(Student study)

SHORT STUDY TITLE / ACRONYM
Audiovestibular function in infratentorial superficial siderosis AViSS

PROTOCOL VERSION NUMBER AND DATE
Version 1.2 Date 16/12/19

RESEARCH REFERENCE NUMBERS

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PROTOCOL VERSIONS

Version Stage	Versions No	Version Date	Protocol updated & finalised by;	Appendix No detail the reason(s) for the protocol update
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LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CI	Cochlear Implant
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
ENT	Ear, Nose and Throat
GAfREC	Governance Arrangement for NHS Research Ethics
HA	Hearing Aid
HTA	Human Tissue Authority
IB	Investigator Brochure
ICF	Informed Consent Form
iSS	Infratentorial Superficial Siderosis
MD	Medical Device
ISRCTN	International Standard Randomised Controlled Studies Number
NHNN	National Hospital for Neurology and Neurosurgery
PI	Principle Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Clinical Study
REC	Research Ethics committee
RNTNEH	Royal National Throat Nose and Ear Hospital
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
SSI	Site Specific Information
TMF	Trial Master File

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STUDY SUMMARY

Study Title	**CLINICAL AND IMAGING BIOMARKERS OF AUDIO-VESTIBULAR FUNCTION IN INFRATENTORIAL SUPERFICIAL SIDEROSIS**
Internal ref. no. (or short title)	Audiovestibular function in infratentorial superficial siderosis (AViSS)
Study Design	Observational study
Study Participants	1) Siderosis group: participants with known diagnosis of infratentorial superficial siderosis; 2) Age-related hearing loss group: participants with known age-related hearing loss; 3) Control group: participants with no known or previously reported hearing loss;
Planned Size of Sample (if applicable)	60-90 participants in total: 20-30 participants - siderosis group 20-30 participants - age-related hearing loss group 20-30 participants - control group
Follow up duration (if applicable)	12 months
Planned Study Period	3 years
Research Question/Aim(s)	(1) To systematically review the literature on audiovestibular function in iSS including most up-to-date available treatment options (2) To comprehensively assess the profile of audiological and vestibular dysfunction in iSS including its impact on the quality of life in comparison to that of age-related hearing loss and the control groups (hearing function) and normative data (balance/vestibular function); (3) To correlate the pattern and degree of hearing loss and vestibular dysfunction in iSS with the imaging findings and other clinical parameters;

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	**FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN**
NIHR UCLH BRC	Grant number BRC-1215-20016-546624
Bernice Bibby Research Trust 34 Homestead Road, Orpington, BR6 6HW (Registered Charity No)	Awarded 1058703
UCL Ear Institute	Administers grant, test facilities

ROLE OF STUDY FUNDER

NIHR UCLH BRC does not control the final decision regarding study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITTEES /GROUPS & INDIVIDUALS

Study Steering Groups

The Chief Investigator (CI) and secondary academic supervisors (study co-investigators) act as a study steering group for study coordination and conduct.

SPONSOR: The sponsor is responsible for ensuring before a study begins that arrangements are in place for the research team to access resources and support to deliver the research as proposed and allocate responsibilities for the management, monitoring and reporting of the research. The Sponsor also has to be satisfied there is agreement on appropriate arrangements to record, report and review significant developments as the research proceeds, and approve any modifications to the design.

FUNDER: The funder is the entity that will provide the funds (financial support) for the conduction of the study. Funders are expected to provide assistance to any enquiry, audit or investigation related to the funded work.

CHIEF INVESTIGATOR (CI): The person who takes overall responsibility for the design, conduct and reporting of a study. If the study involves researchers at more than once site, the CI takes on the primary responsibility whether or not he/she is an investigator at any particular site.

The CI role is to complete and to ensure that all relevant regulatory approvals are in place before the study begins. Ensure arrangements are in place for good study conduct, robust monitoring and reporting, including prompt reporting of incidents, this includes putting in place adequate training for study staff to conduct the study as per the protocol and relevant standards.

The CI is responsible for submission of annual reports as required. The Chief Investigator will notify the RE of the end of the study, including the reasons for the premature termination. Within one year after the end of study, the Chief Investigator will submit a final report with the results, including any publications/abstracts to the REC.

PRINCIPLE INVESTIGATOR (PI): Individually or as leader of the researchers at a site; ensuring that the study is conducted as per the approved study protocol, and report/notify the relevant parties – this includes the CI of any breaches or incidents related to the study.

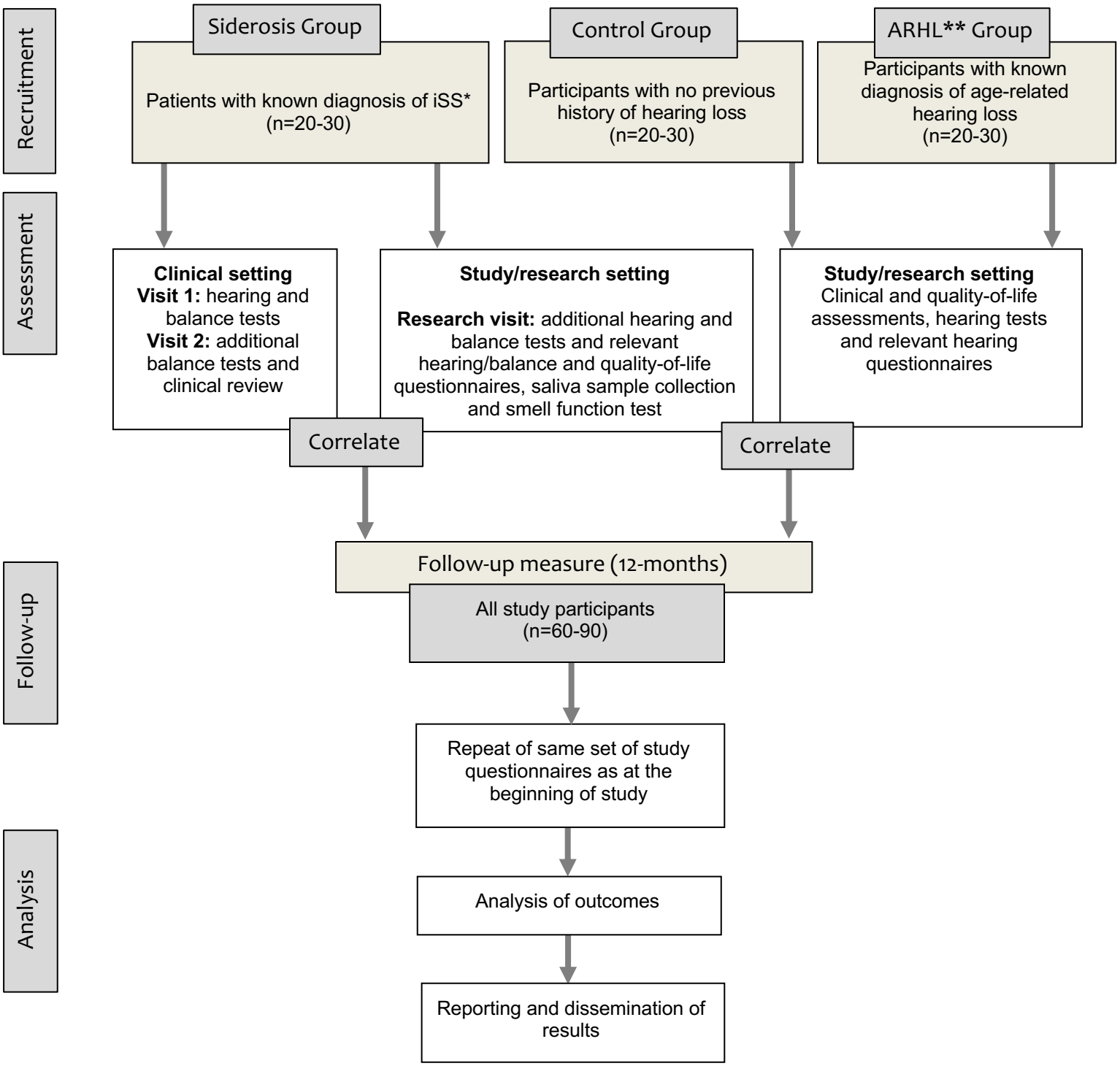
RESEARCH STUDENT/STUDY CO-ORDINATOR: the person who carries out the research study, including: (1) identifying suitability of potential participants to take part in the study, (3) obtaining formal consent from the participants, (2) arranging participants visits, (4) carrying out the assessments and procedures outlined in the protocol, (5) collecting and analysing the data, (6) results write-up and (7) dissemination.

ACADEMIC CO-SUPERVISOR: the person who contributes to the study conception, including the scientific rationale, as well as design, study methodology, feasibility, conduct, reporting of the study and supervises the research student and his/hers research activity.

KEY WORDS:

- Superficial siderosis, infratentorial
- Nervous system diseases
- Auditory pathways
- Hearing tests
- Vestibulocochlear nerve
- Vestibular function tests
- Hearing loss
- Ataxia
- Biomarkers

STUDY FLOW CHART



*Infratentorial Superficial Siderosis (iSS)
**Age-related Hearing Loss (ARHL)

STUDY PROTOCOL

1. BACKGROUND

One in six people in the UK, and over 400 million people worldwide according to the World Health Organisation have disabling[1] hearing loss. These figures are predicted to increase to over 600 and 900 million by 2030 and 2050 respectively (1). However, our understanding of progressive hearing loss is limited and remains the focus for worldwide research.

The current widely accepted and most commonly used method of hearing assessment remains to be pure tone audiometry (PTA). There is, however, a growing body of evidence that PTA is not reflective of true hearing impairment, as it is not representative of the function of the entire auditory pathway (2). The audiological tests (or their combination) that best characterise the overall and disease-specific hearing loss are yet to be determined. The use of speech in noise tests has been previously recognised as a more accurate measure of hearing as it best resembles hearing function in day-to-day life. Speech in noise tests however are not routinely used in the clinical setting. In addition, two most common maskers (types of background noise) used in the speech in noise tests are steady-state speech and background babble. The latter has been demonstrated to be a more sensitive marker of changes in speech discrimination ability and has more face validity, as these testing conditions more realistically resemble real life-situations (3-5).

In the face of increasing prevalence of hearing impairment, there is an urgent need to improve our knowledge regarding hearing loss, its underlying mechanisms, diagnostic methodology, preventative and rehabilitative measures. Together with that comes the need to identify optimal functional and imaging biomarkers and tests that can accurately and reliably identify the site-of-lesion and measure hearing dysfunction.

While our scientific knowledge of the major factors responsible for this increase in the prevalence of hearing loss (both noise-induced and age-related hearing loss, ARHL) is rapidly expanding, our understanding of several less frequent causes of hearing loss of progressive nature remains limited (1).

[1] WHO define disabling hearing loss as hearing loss greater than 40dB in the better hearing ear (adults) and greater than 30dB in the better hearing ear (children)

Superficial siderosis (infratentorial, iSS) is one such condition implicated in progressive disabling hearing loss. It arises from deposition of iron along the surfaces of the brain and spinal cord (6-8). Chronic or repetitive leak of blood into the subarachnoid space leads to accumulation of iron in the sub-pial layers and subsequent neuronal loss, gliosis and demyelination (7, 8). It has been considered uncommon until the advent of Magnetic Resonance Imaging (MRI) which has contributed to increased diagnoses of iSS (9).

The prevalence of superficial siderosis of the CNS has been compared to that of multiple sclerosis, with the respective figures reported at 0.15 and 0.19 percent (10-12) and reported at 0.56 and at 0.7 percent in population-based studies from Minnesota by Pichler et al and the Netherlands by Vernooij et al (cortical superficial siderosis) (13, 14). The prevalence of superficial siderosis in the UK is currently unknown.

Two types of haemosiderosis within the CNS are recognised: supratentorial (cortical) and infratentorial. Both constitute distinct entities and differ in their clinical, radiological and pathophysiological characteristics, although both patterns have been reported to co-exist (7, 15, 16). In cortical (supratentorial) superficial siderosis (cSS), which is often associated with cerebral amyloid angiopathy, the haemosiderin deposits are distributed in the supratentorial pattern and are limited to the cerebral hemispheres (16-18). Hearing impairment or symptoms of imbalance or ataxia are rarely reported in this group.

In contrast, infratentorial superficial siderosis (iSS) is characterised by progressive (often moderate-to-severe) sensorineural hearing loss (SNHL), poor balance and anosmia (8). The infratentorial structures such as cerebellum, brainstem and vestibulocochlear nerve appear to be most susceptible to haemosiderin deposits resulting in the clinical presentation of auditory and balance dysfunction (6-8, 19). Although it can occur at any age, it has frequently been reported in middle-to-older age patients (8, 20). This is likely to be due to its insidious onset and protracted course (often lasting decades), which can contribute to late diagnosis, and significant morbidity may be established by then (8, 10, 11).

Currently, studies that provide comprehensive analyses of auditory and vestibular function in iSS are few. Our knowledge regarding the impact of iSS on the audio-vestibular function is limited to case reports and case series, with patient numbers reported mainly in single figures. The largest two studies to date are by Sydlowski et al and Takeda et al, comprising of ten participants in each,

focusing on audiological and vestibular findings (10, 21, 22). The largest cohort of patients with iSS with hearing loss and ataxia symptoms was reported by Wilson et al from the National Hospital for Neurology and Neurosurgery (NHNN), London, which included 65 patients (7). This, however, was in part a retrospective study focusing on imaging findings, aetiology and diagnostic pathway of assessment. The information on audiovestibular symptoms was obtained from the medical records and it is likely that audiovestibular dysfunction was under-ascertained in this cohort.

In the literature that is available, there appears a lack of uniformity in the audiological and vestibular assessments of patients with iSS. The majority of reports describe the findings of pure tone audiometry (PTA) and characterise the hearing loss as bilateral sensorineural, which can be asymmetric and of variable degree – from mild to moderate to profound – usually with sparing of lower frequencies (8, 10, 21, 23, 24). These reports liken the pattern of hearing loss in iSS to age-related hearing loss (ARHL), when compared on the basis of pure-tone audiogram (10, 25).

Some studies and case reports have included findings of auditory brainstem evoked responses (ABRs) (8, 25-32) as well as speech audiometry (23, 26, 31, 33-36), acoustic reflexes (8, 27, 29), oto-acoustic emissions (OAE) (27-29, 33, 35), and electrocochleography testing (ECoG) (25, 34). In these, hearing loss is reported to be predominantly of retro-cochlear origin, with variable stapedial reflexes and ABR findings (8, 21, 27, 29).

The reports of balance assessment in iSS appear to be fewer, compared to the volume (albeit small) of the audiological reports (22). Where such reports are available, the vestibular test battery is not fully described nor appears to be uniform. While a few studies report on electronystagmography (ENG) findings (23, 27, 30), some also describe vestibular evoked myogenic potential (VEMP) (37) testing and video head impulse testing (v-HIT) (28, 38, 39). The reports describe mixed vestibular dysfunction– with both central and peripheral involvement (30, 40, 41).

In addition to the audiological and vestibular dysfunction associated with iSS, cognitive impairment has also been reported as one of the myriad symptoms associated with iSS (8, 42) yet few dedicated studies provide detailed assessment (29, 43). In a dedicated case series of six patients, van Harskamp et al identified deficits in speech production, executive functioning and visual recall

memory (29), whereas deficits in other cognitive domains have also been described in a number of case reports (43-45).

Greater availability and accessibility of MR imaging has resulted in more frequent recognition of the radiological features of iSS: hypo-attenuating rims along the surfaces of the brain, brainstem, and spinal cord in close proximity to the CSF, including the cerebellar folia, and along the vestibulocochlear nerves (7, 9, 46). MRI brain (and often MRI spine) has now become the modality of choice to investigate ataxia and SNHL in patients in whom the diagnosis of iSS is suspected (7, 9, 46). Computerised tomography (CT) has been shown to be less sensitive and less specific than MRI (8, 46).

Despite the increased recognition and detection of iSS on MRI, close correlation of radiological findings and audiovestibular function in patients with iSS, has not been previously reported. No radiological studies to date have attempted to localise the affected segment of the audiological and vestibular pathways or to correlate the audiovestibular dysfunction with the findings on imaging.

The diagnosis of iSS and the presence of active bleeding into the cerebrospinal fluid (CSF) can be confirmed by examining CSF for iron degradation products and the presence of red blood cells. Some patients exhibit heavy loads of these components on CSF analysis. It is not yet established whether these would correlate with symptom load.

The current treatment of iSS centres on removing the source of bleeding through a number of mechanisms, including ablation of the culprit vessel, repair of dural defect or excision of the offending lesion (42, 47, 48). The non-surgical treatment may include use of iron-chelating agents such as Deferiprone and its use in siderosis patients has demonstrated some degree of improvement in balance symptoms as well as radiological features on longitudinal imaging studies (49, 50). The use of deferiprone, however, has also been linked with the risk of agranulocytosis and neutropenia (8, 46, 47, 51, 52).

Hearing improvement measures for patients with iSS have been limited to conventional hearing aiding and hearing rehabilitation. Cochlear implantation (CI) in iSS patients has been previously described, yet mixed results were reported regarding its benefit (33, 53-55).

In summary, our knowledge of the impact of iSS on audio-vestibular and other functions is limited. Specifically, the diagnostic value of the current battery of audiovestibular tests and their correlation with the radiological findings and other clinical parameters in iSS, including CSF results, in iSS needs to be determined. In addition, it remains to be determined what audiological tests or their combination would best characterise hearing impairment in iSS when compared to individuals with no previous history of hearing loss and to the individuals with age-related pattern of hearing loss. Thus, further studies with larger patient cohorts with iSS as well as studies that employ comprehensive battery of audiological tests and imaging and other clinical tests are needed to reliably identify and quantify hearing dysfunction and its mechanism in iSS.

2. RATIONALE

Presence of progressive and disabling sensorineural hearing loss (SNHL), imbalance and ataxia are the most common clinical features associated with iSS (8). Yet few reports in the literature provide a detailed description of these characteristics. We hypothesise that due to limited knowledge, iSS is likely to be under-recognised in the clinical setting, and thus under-diagnosed and under-reported. Further studies with larger patient cohorts and comprehensive battery of audiological and vestibular tests are required to gain greater understanding and knowledge regarding functional deficits in iSS.

Literature reports describe the pattern of hearing loss in iSS on pure-tone audiometry (PTA), to be similar to age-related hearing loss (ARHL) – down-sloping pattern with the initial loss at higher frequencies. What differentiates the auditory impairment in iSS, is the asymmetrical pattern and earlier onset of hearing loss than expected for ARHL(10). Similarities of pattern of hearing impairment between iSS and ARHL are likely to lead to iSS being misdiagnosed, and may result in disease progression and delayed diagnosis. When assessing the auditory function in iSS with ABR, speech audiometry and stapedial reflex testing, the literature suggests that hearing loss is of retro-cochlear origin.

Due to the lack of reports of comprehensive audiological assessment, the distinct pattern of hearing impairment in iSS patients remains to be elucidated. We hypothesise that the audiological profile of patients with iSS differs from that of individuals with ARHL and that a specific and pathognomonic audiological pattern attributable to iSS may exist. We further hypothesise that pure tone audiometry alone cannot reliably characterise the hearing dysfunction in iSS and that the use of extended audiometric battery of tests is needed to identify the precise audiological deficits in iSS.

We also hypothesise that there will be a greater deficit in speech-in-noise tests in iSS group compared with the ARHL and the control groups, when controlling for hearing deficits and that the speech-in-noise tests are better predictors of hearing dysfunction in iSS than PTA alone or with speech-in-quiet testing. We thus anticipate that speech-in noise tests will account for greater auditory deficits and will better correlate with patient-reported auditory difficulties than PTA and speech-in-quiet tests. We also anticipate a words-in-background babble test will be more able to predict auditory and cognitive impairment in iSS patients than a words-in-background speech noise.

Due to limited volume of literature that describes vestibular function in iSS and its heterogeneity in the battery of tests used, there is a need to provide a comprehensive description of vestibular function in these patients. We hypothesise that balance dysfunction will be due to a mixed (peripheral and central) vestibular deficits and that there will be a greater number of central and oculo-motor abnormalities detected in iSS patients when compared to normative data (40, 41).
We also hypothesise that audiovestibular dysfunction will be identified in the majority of iSS patients after the initial radiological diagnosis and that these deficits will correspond to the involved structures of the auditory and vestibular pathways as visualised on brain images. Correlating the findings of assessments performed with the brain imaging would increase our understanding of the role of imaging in identification of the involved structure(s) of the audiovestibular pathways in iSS.
Additionally, other clinical parameters may also be reflective of the symptom load or the degree of audiovestibular dysfunction and disease progression, and we would like to correlate the results of clinical tests performed in the clinical setting, including MRI, with the audiovestibular findings.

It is likely that iSS and its associated progressive and debilitating hearing and balance impairment) have a negative impact on quality of life. To our knowledge, this has not been reported in the literature and further studies are required to determine this. We will therefore assess the impact of iSS on the quality of life in patients with iSS.
Additionally, 20 percent of iSS patients were reported to have cognitive impairment by Kumar et al yet literature reports of cognitive assessment in iSS are few (56). The cognitive dysfunction may be specific to iSS or due to progressive hearing impairment or a combination of both, and further studies are required establish this. Similarly to cognitive function, olfaction has been reported to affect patients with iSS in 17 percent of patients, yet is rarely reported in the literature (8). We therefore will assess the olfactory function and will use (University of Pennsylvania) Smell Identification Test (SIT).
We further hypothesise that there is a genetic predisposition to the development of iSS which may contribute to the degree of associated symptoms. We will collect the saliva samples from the iSS participants (self-collected) to biobank the DNA for genetic analysis during this study or for use in other or future studies.

As part of this study we will collect self-report measures, such as Modified Amsterdam Inventory for Auditory Disability and Handicap (mAIADH), Speech, Spatial and Qualities of Hearing Scale (SSQ) questionnaire and Tinnitus Functional Index (TFI) adjunct the auditory tests, and Dizziness Handicap Inventory (DHI) and Situational Vertigo Questionnaire (SVQ) alongside the vestibular tests. We hypothesise that these will reflect symptom load and may reflect functional deficits (as

identified on auditory, vestibular and cognitive tests), and we will correlate these with disease severity and the degree of functional impairment.

Because iSS is characterised by auditory and vestibular dysfunction which are reported to be disabling and debilitating it is also important to assess this over time. We hypothesise that the use of interval hearing and balance (vestibular) questionnaires in iSS participants may reflect changes in these functions, which may also be reflective in the quality-of-life questionnaires in these participants, and thus these can be used as a functional outcome measure to monitor disease progression and in the future research and clinical settings – to monitor response to treatment. We hypothesise that these can be used as an adjunct measure of degree of dysfunction and iSS progression than the currently available techniques, including imaging (57).

This will be one of the largest studies to date focusing on functional deficits in iSS, and will provide a detailed phenotype of its audiological and vestibular functions. The comprehensive test battery will allow to determine the accurate and disease-specific pattern of hearing and balance impairment in iSS. This in turn may lead to iSS being more frequently recognised, promptly diagnosed and timely initiation of treatment. In this study we will attempt to identify the tests that best measure functional impairment in iSS and can thus be used to assess the severity, and as a means of monitoring disease progression and the response to treatment. In addition, the study results will inform us regarding the most suitable and likely beneficial rehabilitative measures that can be offered to symptomatic patients with iSS in the clinical practice in the future.

This project will thus enhance our overall understanding and knowledge of hearing loss and imbalance, cognitive and olfactory functions in patients with iSS. By involving a larger cohort of patients which has previously been described by Wilson et al (7), we will be able to draw similarities with the reports evidenced in the literature and compare the findings to those of the age-matched individuals with ARHL and the control groups in the study. In addition, the use of comprehensive battery of hearing tests between the groups will help to determine tests that best identify and quantify auditory dysfunction. We will also be able to compare the results to the normative data and attempt to establish the impact of iSS on quality of life in comparison to individuals with age-related hearing loss and control group. This study will contribute to the global pool of knowledge regarding iSS and may improve understanding of this condition. This in turn may help inform research regarding means of diagnosis, management and rehabilitative measures, and monitoring of disease progression and treatment responses of audiovestibular dysfunction in iSS patients.

3. THEORETICAL FRAMEWORK

Because our knowledge of the impact of iSS on hearing and balance is limited and due to progressive and significant morbidity associated with this condition, there is a clear need to improve our understanding of audiovestibular dysfunction and determine its disease-specific pattern. Early recognition of iSS in the clinical setting will enable prompt efforts to halt disease progression by means of initiation of treatment and rehabilitative measures and as a consequence, likely reduction in the associated morbidity.

Extensive battery of hearing tests, including self-report questionnaires, undertaken by the participants will identify test-specific deficits and will reflect which of the tests or their combination best characterise auditory dysfunction in iSS, how these deficits compare to the auditory characteristics in the ARHL group, and which tests most accurately identify hearing dysfunction in both groups. The use of self-report questionnaires in combination with the psychophysical tests will further characterise the auditory and vestibular dysfunction and are thus likely to better reflect functional deficits specific to iSS and ARHL than by means of objective tests alone.

This analysis will achieve a dual goal: firstly, we will be able to determine the disease-specific pattern of hearing loss in iSS and how it compares to age-related hearing loss; and secondly, we will be able to determine which tests or their combination best reflect auditory dysfunction in patients with hearing impairment and are thus likely to be used as markers of function and outcome measures in assessment of sensorineural hearing loss. By employing an extended battery of audiological tests and their combination, we will also attempt to stratify patients with hearing problems based on the likely site of pathology of the auditory pathway and identify those with peripheral deficits from patients with central deficits.

A better understanding of the mechanisms responsible for the patients' audiovestibular symptoms and better localisation of the likely site of pathology within the auditory pathway could have a significant impact on the clinical practice for patients with iSS and for patients with age-related hearing impairment. This study will provide information on the value of audiological and vestibular assessments in iSS and which of those can be applied in the future clinical and research settings as a measure of disease progression and the response to treatment.

4. RESEARCH QUESTIONS/AIMS

Aims

The aims of this study are:

1. To systematically review the literature on audiovestibular function in iSS, including most up-to-date available treatment options;
2. To comprehensively assess the profile of audiological and vestibular dysfunction and its impact on quality of life in iSS in comparison to that of age-related hearing loss (ARHL) and the control groups;
3. To correlate the pattern of hearing loss and vestibular dysfunction in iSS with the imaging findings;

4.1 Objectives

1. To determine the audiological and vestibular deficits in patients with iSS and compare these to ARHL and control groups, and to normative data (vestibular function, siderosis group);

2. To correlate the functional deficits and the likely affected structures of auditory and vestibular pathways with brain imaging findings (siderosis group);

3. To determine what combination of tests (including questionnaires) best characterise, quantify and differentiate the auditory dysfunction in the two groups and which tests can be used as optimal outcome measures for diagnosis, monitoring of hearing dysfunction and for hearing rehabilitation;

4. To assess the impact of iSS on quality of life and other functions (olfactory and cognitive) by administering quality of life questionnaires and the Smell Identification Test (SIT) as part of this study. Neuropsychological assessment will be performed as part of clinical care pathway;

4.2 Outcome questions

Primary outcome question: What are the salient and disease-specific features of auditory and vestibular dysfunction and what is the impact of iSS on olfactory and cognitive functions and on the quality of life?

Secondary outcome question: How do the imaging findings correlate with the results of audiological, cognitive and vestibular assessments and severity of symptoms?

Tertiary outcome question: Which audiological tests are able to better predict auditory impairment in iSS group compared to the ARHL and the control groups?

Quaternary outcome question: Can a combination of auditory testing approaches be used as a valid functional tool for hearing assessment and site of lesion testing in patients with auditory dysfunction based on the findings of the cohorts included in this study?

5. STUDY DESIGN, METHODS of DATA COLLECTION AND DATA ANALYSIS

5.1 Study design

This will be an observational study in which three cohorts of participants (two with a known condition, third as a control cohort) will be recruited (58). The auditory function in patients with infratentorial superficial siderosis (iSS) will be compared to the age-related hearing loss (ARHL) group and to the control group with no previous history of hearing loss.

The study protocol has been designed by the Chief Investigator, the study co-investigators/academic supervisors and the research student (study co-ordinator). The STROBE guidelines and checklist for reporting observational studies have been consulted when developing the study protocol (59). Prior to undertaking the study, the protocol has been reviewed by the academic sponsor and is in line with the site-specific regulations.

5.2 Data collection methods

All study participants who meet the criteria and have given formal informed consent to take part in this study will undergo the investigations as set out in this study protocol. All research investigations as set out in this protocol will be performed by the research student and/or a designated (and appropriately trained) research nurse and/or designated (and appropriately trained) research audiologist. Because these investigations are used in the clinical practice in the NHS, these may be performed as part of the routine clinical care pathway and in such instances the research student will only complete the investigations which have not been performed during the clinical assessment.

The research student (who is clinically trained) will have the skill, capacity and indemnity to carry out the study assessments. The Chief Investigator will ensure that the research student will have received appropriate training where necessary to carry out the study assessments.

Each participant will be asked permission to notify his or her primary health care team/GP of the involvement in the study. Each participant will be asked if they would like to be made aware of any significant clinical findings identified in the course of the study and whether they would like their primary health care team/General Practitioner to be notified of the findings so that the referral to appropriate services can be made. The participant's decision will be documented in the participants' medical notes (where applicable) and study file during the initial consultation and ahead of any testing taking place. Should the participant not wish to be made aware of any

significant findings during the study, the research student will enquire and ask permission to notify his/hers next of kin and/or the primary care team/GP. Neither the siderosis group participants who consent to saliva sampling and DNA testing nor their primary care teams/GP will be notified of the genetic testing results during the study and as part of other/future studies.
Participants' consent will be sought to access their clinical notes including other tests carried out to date in order to collect the data from their clinical notes in anonymised format and to avoid repeating the tests already performed in the clinical setting.

Investigations:

Following the recruitment procedure and after giving the formal informed consent, all study participants will undergo clinical and hearing assessments and complete a set of validated hearing and quality-of-life questionnaires (detailed description below). In addition, the siderosis participants will undergo assessments of the balance (including balance questionnaires) and olfactory functions, and saliva sampling (in an anonymised format) for DNA banking for iSS. The anonymised saliva samples may be used for other/future research studies. Results of cognitive, imaging and other clinical assessments will be performed as part of the clinical care pathway and will not be assessed as part of this research project. However, their results may be used in the anonymised format as part of this research study.

The ARHL group and the control group participants will require one assessment session whereas the siderosis group participants will require three sessions in total (two of which will be standard part of the clinical care pathway).

Siderosis group visits and investigations:

Siderosis group participants will be seen by the clinical team as part of their clinical care pathway and will undergo the following tests during their **first/initial visit in the Neuro-otology clinic:**

1. *Informed consent*
2. *Full neuro-otological examination:* full medical history; clinical examination of the head and neck, ears (otoscopy) and cranial nerves III/IV/VI/VII, (20mins)
3. *Pure tone audiometry (PTA)* for each ear measuring air and bone-conduction (15mins)
4. *Screening tympanogram* to check the function of the middle ear (5mins)
5. *Auditory Brainstem response (ABR) testing* on a calibrated ABR system; recorded with monaural alternating click stimuli; minimum intensity of 90dB (40mins)
6. *Vestibular nystagmography (VNG)/rotational chair testing*: including eye tracking/gaze nystagmus/positional nystagmus/optokinetic nystagmus/smooth pursuit/saccade tests (30mins)

7. *Video Head Impulse Test (vHIT):* using appropriate software, goggles and in-built video-camera to record eye movements during unpredictably-timed and -directed head-rotations at speed 150-300degree/s (10mins)

At the first clinic visit the siderosis group the participants who have expressed interest in participating in the study will be seen by the research student. After confirming their eligibility and willingness to participate in the study, the potential participants will be formally consented and enrolled in the study. The research student and the study participant will arrange a suitable date/time for the research visit to take place.

During the research visit, the siderosis group participants will undergo the following:

1. Verification of the participant's eligibility to participate in the study and that the informed consent has been obtained (5mins)
2. Brief medical history and clinical examination (of ears/eyes/co-ordination) (5mins)
3. *Speech-in-quiet test* (10mins)
4. *Otoacoustic emissions (OAEs)* by delivering sound stimuli through a probe in the ear canal, using dual channel analyser (10mins)
5. *Stapedial (acoustic) reflex thresholds*: ipsilateral (same side) and contralateral (opposite side) measurements using a calibrated middle ear recorder at 0.5/1/2/4 kHz; range 70-120dB HL (5mins);
6. *Speech-in-noise testing:* a set of tests with background noise/speech/babble, administered using appropriate programme through headphones, where words/sentences/speech presented in competing background noise/speech/babble (50-60mins)
7. *Functional Gait Assessment (FGA):* assessment of postural stability; 10-point test, incorporating (head) turns, gait changes (that would usually include speed, narrow base, stairs, backwards, level, obstacles) (10mins)
8. *Scale for Assessment and Rating of Ataxia (SARA):* clinical scale to assess cerebellar ataxia which is made up of 8 items related to gait, stance, sitting, speech, finger-chase test, nose-finger test, fast alternating movements and heel-shin test (15mins)
9. *Olfactory (smell) Smell Identification Test (SIT)*: self-administered test, a booklet with odour-impregnated pages; the odour is introduced to the tester by scratching the test booklets (10mins)
10. *Saliva sampling* for DNA biobanking (max 30ml, equivalent of the volume of maximum two table-spoons) (5mins)

11. *Hearing questionnaires* (which can be distributed to the participant ahead of the appointment and collected during their visit, after having given formal consent to participate in the study, as a time saving measure)
    - *Modified Amsterdam Inventory for Auditory Disability and Handicap (mAIADH) questionnaire*: a 28-point self-report questionnaire that assesses listening ability on 5 domains (5mins)
    - *Speech, Spatial and Qualities of Hearing Scale (SSQ) questionnaire;* contains 50 items and involves 3 hearing domains, namely: speech, spatial and qualities (of sound segregation and identification) (5mins)
    - *Tinnitus Functional Index (TFI) questionnaire*; 25-item self-report questionnaire; has been shown to have higher validity than other tinnitus questionnaires (5mins)
12. *Vestibular questionnaires* (which can be distributed to the participant ahead of the appointment and collected during their visit, after having given formal consent to participate in the study, as a time saving measure) and will include:
    - *Dizziness Handicap Inventory (DHI):* self-report questionnaire on perceived impact of dizziness on daily life assessing (5mins)
    - *Situational Vertigo Questionnaire (SVQ):* self-report 19-item questionnaire that measures frequency of symptoms of disorientation/vertigo against visually busy environment (5mins)
13. *Quality-of-life questionnaires* (which can be distributed to the participant ahead of the appointment and collected during their visit, after having given formal consent to participate in the study, as a time saving measure). The quality of life will be assessed using three validated quality-of-life questionnaires:
    - *Health Utilities Index-3 (HUI3)* (5mins)
    - *EuroQoL Questionnaire (EQ-5D-5L)* (5mins)
    - *Evaluation of the Impact of Hearing Loss in Adults (ERSA)*

A follow-up clinical appointment will be also arranged for the siderosis patients (irrespective of their participation in the study). During their follow-up clinical visit, the siderosis patients will undergo the following clinical assessments, as part of their clinical care:

1. *Vestibular evoked myogenic potentials (VEMP)*: calibrated auditory stimuli via ear inserts repetitively presented and neck/eye myogenic (muscle) responses are recorded (20mins)

2. The siderosis patients who have previously consented to participate in the study will then be seen by the research student and the *questionnaires* previously distributed to the study participants will be collected (5mins)

Appropriate break times will be given to the participants during their research study visit. It is anticipated that the total time to complete the assessments will be approximately two to three hours for each visit.

Where the research tests have been completed by the audiologist/clinician/nurse, the research student shall not repeat those during the respective visit but will instead include the results of the tests already performed. Where the clinical tests have not been carried out by the clinical staff (audiologist/clinician/nurse), the research student will carry these out as part of the clinical care pathway and will include the results obtained from the clinical assessments.

Cognitive function will be assessed by means of neuro-psychological testing in line with the clinical care pathway and will be arranged by the clinical team. Imaging will be arranged by the clinical team in line with the clinical care pathway for siderosis patients. With the prior consent obtained from the participants, the results of the clinical assessments (including cognitive and imaging tests) will be obtained and anonymised at source.

<u>Age-related hearing loss group and control group participants' visits and investigations:</u>
The age-related hearing loss group and control group participants will undergo the clinical and hearing assessment (including hearing questionnaires) and quality-of-life questionnaires during one visit only. All the tests will be done as part of this research study.

During their visit, the ARHL group and control group participants will undergo:

1. Informed consent
2. *Full neuro-otological examination* (full medical history; clinical examination of the head and neck, ears (otoscopy) and cranial nerves III/IV/VI/VII)
3. *Pure tone audiometry (PTA),* for each ear measuring air and bone-conduction (15mins)
4. *Otoacoustic emissions (OAEs),* by delivering sound stimuli through a probe in the ear canal, using dual channel analyser (10mins)
5. Speech in quiet test (10mins)
6. *Stapedial (acoustic) reflex thresholds*: ipsilateral and contralateral measurements using a calibrated middle ear recorder at 0.5/1/2/4 kHz; range 70-120dB HL (5mins);

7. *Auditory brainstem evoked response (ABR) testing*, on a calibrated ABR system; recorded with monaural alternating click stimuli; minimum intensity of 90dB (40mins)
8. *Speech in noise testing,* a set of tests with background noise/speech/babble, administered using appropriate programme through headphones, where words/sentences/speech presented in competing background noise/speech/babble (50-60mins)
9. *Hearing questionnaires* (which can be distributed to the participant ahead of the appointment and collected during their visit, after having given formal consent to participate in the study, as a time saving measure), including:
    - *Modified Amsterdam Inventory for Auditory Disability and* Handicap (mAIADH) *questionnaire:* a 28-point self-report questionnaire that assesses listening ability on 5 domains; (5mins)
    - *Speech, Spatial and Qualities of Hearing Scale (SSQ) questionnaire*; contains 50 items and involves 3 hearing domains, namely: speech, spatial and qualities (of sound segregation and identification) (5mins)
    - *Tinnitus Functional Index (TFI) questionnaire*; 25-item self-report questionnaire; has been demonstrated to have higher validity than other tinnitus questionnaires (5mins)

10. *Quality-of-life questionnaires* (which can be sent out to the participant ahead of the appointment and collected during their first visit, after having given formal consent to participate in the study, as a time saving measure). The quality of life will be assessed using two standard quality-of-life questionnaires:
    - *Health Utilities Index-3 (HUI3)* (5mins)
    - *EuroQoL Questionnaire (EQ-5D-5L)* (5mins)
    - *Evaluation of the Impact of Hearing Loss in Adults (ERSA)*

Appropriate break times will be given to the participants during their testing at the research study visit. It is anticipated that the total time to complete the assessments will be approximately two to three hours.

Follow-up Investigations:

As a follow-up measure, all study participants will undertake a repeat set of self-report questionnaires after 12 months of their initial completion of the questionnaires (as what would have been completed by the participants at the beginning of the study). These will be sent out to the participants with pre-stamped self-addressed envelopes and will be returned to the research facility by post, or distributed and collected electronically.

The assessments of the siderosis group participants will take place at University College London Hospitals (NHS Foundation Trust). The assessments of the participants from the ARHL group and control group will take place at University College Hospitals (NHS Foundation Trust) London and/or the UCL Ear Institute, depending on the availability of the testing facilities.

The data will be collected and analysed using a dedicated statistical software programme (package) to determine disease-specific pattern and test deficits in iSS and to compare those to the ARHL and the control groups and to the normative data (vestibular function only).

Interventions:

No formal interventions will be carried out during the course of this study. If clinically indicated, the participants (with their prior consent) will be referred to the Adult Audiology Services for further evaluation and hearing aiding assessment, or to the Ear, Nose and Throat (ENT), Audiovestibular Medicine (AVM) or Cochlear Implant Services at University College London Hospitals (NHS Foundation Trust) for further evaluation and management. The research student will seek formal advice from the Chief Investigator of the study before making the referrals. The referrals will be made following the participant's consent to do so and in accordance with the current clinical guidelines and with the protocol adopted at University College London Hospitals (NHS Foundation Trust). The participant's primary healthcare team/GP will be informed of the referral (with the participant's prior consent obtained to do so).

Comparison:

The findings obtained following the audiological and the quality-of-life questionnaires will be compared between the siderosis group, the ARHL group, and the control group. The results of vestibular assessments will be compared to the age-matched normative data.

Outcomes:

The outcomes will reflect the aims and objectives of the study. These will be recorded by the research student.

Study/Participant Timeline:

Following the Ethical approval to undertake the study, the relevant teams (team at the Neurology Department and the team at the Adult Audiology Services), University College London Hospitals (NHS Foundation Trust) will be informed by the research student of the study taking place. The potential participants will be identified by the relevant clinical teams (siderosis group and ARHL

group) and will be asked by the clinical team members for their consent to be contacted by the research student. To maximise the recruitment, the ARHL group will also be recruited from the general public. The control group will be recruited from the general public. We would like to recruit members of the general public aged 50 or above to closely approximate the age between the groups, however if such recruitment is difficult, we will recruit members of the general public aged 18 and above.

The recruitment will take place simultaneously for all three groups of participants. The recruitment period will be defined from the date the participant information sheet is sent to the potential participant to the participant giving formal consent to take part in the study. Potential participants interested in talking part in the study will be sent out the relevant study participant information sheet (group specific) together with the Data Use Confidentiality Statement and an Invitation Letter ahead of their first visit (to the University College London Hospitals (NHS Foundation Trust) or to the UCL Ear Institute). The first and follow-up visit for (potential) siderosis group participants will take place as part of their clinical appointment in the Neuro-otology Clinic. Additionally, a research appointment will be arranged. For participants from the ARHL and control groups the appointment/study visit will take place at either University College London Hospitals (NHS Foundation Trust) or the UCL Ear Institute, depending on the availability of the testing facilities. The date and time convenient for the participant and the research student will be determined in advance. During the initial/first consultation (siderosis group) /study visit (ARHL and control groups), the research student will obtain formal written consent from the participant and will document this in the medical notes and/or study file. A copy of the signed consent form will be given to the participant.

The research student and the participant (siderosis group participants only) will discuss the research visit and the tests that will take place then and whether the participant is willing to continue their participation in the research project. The research student will then arrange a suitable date/time for the research visit. The clinical follow-up visit will be scheduled by the clinical team and the interval will be decided as clinically necessary.

As a follow-up measure for the research study, all participants will be asked to complete a repeat (identical) set of questionnaires at a 12-month time interval after completing their first set. The identical set of questionnaires will be distributed to the participants by post with a pre-paid self-addressed envelope, or by email and will be returned by post or electronically.

The recruitment will take place over a 24-month period, the assessments and data collection will take place over a 36-month period. The last participant's follow-up appointment is anticipated to be no later than August 2021. The end of the study is defined when the last set of questionnaires is sent-out as a 12-month follow-up measure, whichever one of these events is last. The overall

study duration will be from August 2019 to (end of) July 2022 and will include the time required for data analysis and writing up of the results. Subsequent formal final study report will be put together for the Research Ethics Committee and the sponsor.

5.3 Data collection, management and handling

Following the Ethical approval to undertake the study, the relevant teams (team at the Neurology Departments and the team at the Adult Audiology Services) University College London Hospitals (NHS Foundation Trust) will be informed by the research student of the study taking place. The potential participants will be identified by the relevant clinical teams (siderosis group and ARHL group), and contacted or approached in the clinical setting to ask permission to be contacted by the research student or to establish their decision to participate in the study and to be sent the study invitation letter and participant information sheets. The siderosis and ARHL group participants' contact details (including manual files that contain personal addresses, postcodes, e-mail and telephone numbers) will be kept secured in a locked folder by the participants' healthcare team at University College London Hospitals NHS Foundation Trust. Only the Chief Investigator and the clinical team members will have the key to the folder with the contact details for the participants. Once the participants are recruited onto the study, the participants' contact details (including personal addresses, postcodes, email or telephone numbers) will be kept on a secure UCL data safe haven platform (for participants from all groups).

The creation of coded, depersonalised data where the participant's identifying information is replaced by an unrelated sequence of characters to constitute a unique study ID number for each participant will be in place. No participant personal or identifiable data will be kept by the research student.

Secure maintenance of the data and the linking code in separate locations within lock folders and storage media will be ensured. The digital data collected by the research student will be stored in the UCL secure safe haven data platform with encryption and password protection.

5.4 Material/Sample Storage

In the study, saliva sample will be collected from the siderosis group participants only (to the maximum of 30ml, i.e. the equivalent of the volume of maximum two table-spoons) in accordance with the patient consent form and patient information sheet.

Samples will be collected by the research student and will be anonymised. The samples will be labelled with a unique study code and will not contain identifiable information. The samples will be delivered by the research student to the designated laboratory in accordance with the UCL lab

protocol with which prior contractual agreement for processing and storage has been made. The samples will be stored for the duration of the study (three years). The samples will be processed, stored and disposed of in accordance with all applicable legal and regulatory requirements, including the Human Tissue Act 2004 and any amendments thereafter, and after relevant testing has taken place. Anonymised samples will be stored and used as part of this study but may be used for further testing in other/future studies.

The Chief Investigator will act as the custodian on behalf of UCL who is the data controller. The UCL Ear Institute Human tissue lab, London will store, process, and dispose of the samples.

5.5 Data analysis methods

Quantitative Analysis will be conducted using dedicated statistical software package. Statistical analysis will be performed under the guidance and with advice of a designated biostatistician at UCL and/or at Biostatistics Office, UCL(H) Joint Research Office (JRO). Each variable will be checked for distribution skewness, and regression models for each variable will be constructed. For binary variables, chi-square tests will be performed in order to determine the difference in the findings between the siderosis group and the control groups.

6. STUDY SETTING

After participant recruitment, the study assessments will take place at University College London Hospitals (NHS Foundation Trust) (participants from all groups) or UCL Ear Institute (participants from ARHL and control groups only). The participants for this study will be recruited from:

- University College London Hospitals (NHS Foundation Trust) (siderosis group)
- Adult Audiology Centre, University College London Hospitals (NHS Foundation Trust) (ARHL group)
- The general public (ARHL and control groups): will be recruited from University College London Hospitals (NHS Foundation Trust) waiting areas, canteens, cafeterias, BRC BioResource group, AgeUK group, the University of Third Age and dedicated Facebook/social network and online groups

The clinical equipment available at the Adult Audiology Services at University College London Hospitals (NHS Foundation Trust) or provided by the UCL Ear Institute, will be used to conduct this study. No additional equipment will be provided to sites for the purposes of the study since all the tests in this protocol are already available to the NHS users with hearing impairment, poor coordination or cognitive impairment. The facilities at the Ear Institute permit hearing tests to take place. These can be conducted by the research student and be undertaken by the participants with minimal risk of balance problems and minimal risks of falls such as the ARHL group and control group participants.

7. SAMPLE AND RECRUITMENT

7.1 Eligibility Criteria

Potential participants will be identified by a member of the relevant clinical team or recruited from the general public, and according to the inclusion/exclusion criteria as outlined below. The recruitment will take place simultaneously for all three groups of participants.

7.1.1 Siderosis group

Inclusion criteria:

- Adults (male and female) of 18+ years old with a known diagnosis of iSS confirmed by a consultant neurologist with expertise in this condition at University College London Hospitals (NHS Foundation Trust)

Exclusion criteria:

- Individuals with a physical or mental impairment that prevents the potential participant from giving informed consent or undergoing the audiological and/or vestibular assessment
- Individuals younger than 18 years old
- Individuals with no prior diagnosis of iSS

7.1.2 Age-related hearing loss (ARHL) group

Inclusion criteria:

- Adults (male and female) of 18+ years old with a known diagnosis of ARHL

Exclusion criteria:

- Individuals with a physical or mental impairment that prevents the potential participant from giving informed consent or undergoing the audiological assessment
- Individuals younger than 18 years old
- Individuals with diagnosis of hearing loss of aetiology other than age-related

- Individuals with history of exposure to high-intensity noise or ototoxic drugs or evidence of middle ear disease/dysfunction or family history of non age-related hearing loss
- Individuals with no previous diagnosis of age-related hearing loss

7.1.3 Control group

Inclusion criteria:

- Adults (male and female) of 18+ years old with no previous diagnosis of hearing loss or no known neurological disorder (including iSS) that affects hearing (control group); we will aim to recruit such participants of 50 years of age and above, however if difficulty with recruitment of such participants arises, we will recruit participants of 18 years of age and above.

Exclusion criteria:

- Individuals with a physical or mental impairment that prevents the potential participant from giving informed consent or undergoing the audiological and assessment
- Individuals younger than 18 years old
- Individuals with a known history of hearing loss (of any cause) or with a known neurological disorder that affects their hearing
- Individuals with history of exposure to high-intensity noise or ototoxic drugs or evidence of middle ear disease or family history of non age-related hearing loss

Participants in the siderosis group will be users of the National Health Service (NHS) and will be recruited from University College London Hospitals (NHS Foundation Trust) London. The ARHL group participants will be recruited from the Adult Audiology Services at University College London Hospitals (NHS Foundation Trust), and will have used the NHS services in the past or will be recruited from the general public. The control group participants will be recruited from the general population. There will be no upper limit to the participants' age.

7.2 Sampling

7.2.1 Size of sample

Power and sample size calculations cannot be reliably carried out prior to commencing the study as we are restricted by how rare the disease is. Furthermore, there are currently few reports on audiological and vestibular function in iSS in the literature, and where available, these are highly heterogeneous in the testing regimens used. There appears no primary test or indicator that is considered the 'gold standard' test. This heterogeneity means that it is challenging to effectively perform necessary power/sample size calculations. In addition to this, a comprehensive battery of tests will be included in this study, each of which will influence the required sample sizes. Due to its rarity we would like to recruit as many participants with iSS as possible. Reviewing the study for feasibility, however, after 10-15 participants in each arm have been assessed in the study, will allow to establish the variability between the groups and will be used to inform the adjustment to sample size. Furthermore, it will be likely to reflect on the difficulty (or ease) as well as the pace of recruitment of participants into the study.

These preliminary results will be collected and analysed by the research student in collaboration with a designated biostatistician from the UCL and the Biostatistics Office at UCL(H) JRO. A validated statistical software programme will be used to conduct the analysis, which will include all the parameters and assumptions used in the pilot study. Inflation factors and attrition rate will also be accounted for and will be included into sample size calculations.

7.2.2 Sampling technique

Due to rarity of iSS we would like to include as many participants with this diagnosis as possible (to the maximum of 30 participants). The sizes of other two groups will match the siderosis group sample (to the maximum of 30 participants in ARHL and control groups each).

7.2.3 Sample identification

<u>Siderosis group:</u>

Potential participants will be identified from the clinical database by a member of the Siderosis/Neurology team at University College London Hospitals (NHS Foundation Trust) which is likely to be one of the largest databases in the UK, due to rarity of the disease and the highly specialist expertise of the Neurology team in this area at University College London Hospitals (NHS Foundation Trust).

<u>Age-Related Hearing Loss group:</u>

Potential participants will be identified from the clinical database by a member of the Adult Audiology Services team at University College London Hospitals (NHS Foundation Trust) and will approximate the numbers of the participants in the siderosis group (20-30 participants). Alternatively, and to maximise the recruitment potential, the age-related hearing loss group

participants may be recruited from the general public (by advertising the study and/or displaying the study posters in community hearing aid centres, AgeUK, the University of Third Age, and through the BRC BioResource Bank at UCLH, dedicated Facebook/social network and online groups.

Control group:

Potential participants will be recruited from the general public and will approximate the numbers of the participants in the siderosis group (20-30 participants). In order to best approximate the ages between the groups, we will aim to recruit general public participants of 50 years of age and above, however if difficulty with recruitment of such participants arises, we will recruit participants of 18 years of age and above. The study recruitment posters will be displayed in the public areas such as waiting areas, canteens and cafes in University College London Hospitals (NHS Foundation Trust) or by advertising the study and/or displaying study posters in community hearing aid centres, AgeUK, the University of Third Age, and through the BRC BioResource Bank at UCLH and dedicated Facebook/social network and online groups.

7.3 Recruitment

Three cohorts (of approximately 20-30 participants in each) will be recruited into the study, comprising of:

1. Cohort of participants with the diagnosis of iSS (siderosis group). These will be recruited from University College London Hospitals (NHS Foundation Trust).
2. Cohort of participants with the diagnosis of ARHL (ARHL group). These will be recruited from the Adult Audiology Centre, University College London Hospitals (NHS Foundation Trust) or from the general public (by advertising the study and/or displaying the study posters in community hearing aid centres, AgeUK, the University of Third Age, and through the BRC BioResource Bank at UCLH and dedicated Facebook/social network and online groups.
3. Cohort of individuals with no previous history of hearing problems (control group). These will be recruited from the general population. The study recruitment posters will be displayed in the public areas such as waiting areas, canteens and cafes in University College London Hospitals (NHS Foundation Trust) or by advertising the study and/or displaying study posters in community hearing aid centres, AgeUK, the University of Third Age, and through the BRC BioResource Bank at UCLH and dedicated Facebook/social network and online groups.

Participant's journey from the point of identification to the recruitment into the study (siderosis group):

Patients with the diagnosis of iSS who attend Neurology Clinics at University College London Hospitals (NHS Foundation Trust) will be identified from a prospectively collected patient database of all known referrals with iSS. A member of the clinical team will approach the potential participant in the clinical setting to let them know that the study is taking place and asking their permission to be contacted by the research student. Alternatively, a member of the clinical team will contact the potential participant informing them of the study taking place and asking their permission to be contacted by the research student. If consent is given to be contacted, the research student will send a participant information sheet together with a study invitation letter and a pre-stamped self-addressed envelope to the identified potential participants.

There will be no time-limit to the participants' decision to take part in the study.

If willing to participate, the patients will be contacted by the research student to provide the participant information sheet and the study invitation letter. The study participation schedule will be discussed between the potential participant and the research student and the clinic appointment time (as scheduled by the clinical team) will be confirmed. The first/initial visit will take place during the clinical visit to Neuro-otology services at the University College London Hospitals (NHS Foundation Trust). The research student will ask the potential participant if willing to complete self-report questionnaires at home prior to their visit, and if so, these will be sent out to the potential participant to fill in at home ahead of their visit (as a time-saving measure). These will not be collected only after the written consent has been obtained by the participant to take part in the study.

During the first/initial study visit to University College London Hospitals (NHS Foundation Trust), the participant's questions pertaining to the study will be answered by the research student. The candidate's eligibility to participate in the study will be determined at this point, and the formal written consent to participate in the study will be obtained. The questionnaires that have been distributed to the participants will be collected only after obtaining the formal written consent to take part in the study. No study related procedures will be performed without the participant's consent. The participant's decision to take part in the study will be documented in the medical notes. A copy of the formal written consent will be given to the participant.

Where the participant is ineligible, this, together with the reasons for ineligibility, will be documented by the clinical team member in the participant's medical notes.

Participant's journey from the point of identification to the recruitment into the study (ARHL group):

Patients with the diagnosis of ARHL who previously attended Adult Audiology Centre University College London Hospitals (NHS Foundation Trust) will be identified from the patient database. A member of the clinical team will approach the potential participant in the clinical setting to let them know that the study is taking place and asking their permission to be contacted by the research student. Alternatively, a member of the clinical team will contact the potential participant informing them of the study taking place and asking their permission to be contacted by the research student. If consent is given to be contacted, the research student will send a participant information sheet together with a study invitation letter and a pre-stamped self-addressed envelope to the identified potential participants.

Alternatively, and to maximise the recruitment potential, the age-related hearing loss group participants may be recruited from the general public by advertising the study and/or displaying the study posters in community hearing aid centres, AgeUK, the University of Third Age, and through the BRC BioResource Bank at UCLH and dedicated Facebook/social network and online groups.

The advertisement/study poster will contain the contact details of the research student. Potential participants interested in the study will be able to contact the research student and will be provided with a participant information sheet together with an invitation letter upon contact. There will be no time limit to the participants' decision to take part in the study. If willing to participate, the potential participant will contact the research student and will be invited to attend University College London Hospitals (NHS Foundation Trust) or the UCL Ear Institute. The research student and the potential participant will agree on a suitable appointment day and time. The research student will ask the potential participant if willing to complete self-report questionnaires and if so, these will be sent out to the potential participant to complete at home (as a time-saving measure). These will not be collected until the appointment and only after the written consent has been obtained by the participant to take part in the study.

During the visit to University College London Hospitals (NHS Foundation Trust) or the UCL Ear Institute, the participant's questions pertaining to the study will be answered by the research student. The candidate's eligibility to participate in the study will be determined at this point, and the formal written consent to participate in the study will be obtained. The questionnaires that have been sent out to the participant will be collected at this stage and only after obtaining the formal written consent from the participant to take part in the study. No study related procedures will be performed without the participant's consent. The participant's decision to take part in the study will be documented in the medical notes (where applicable). A copy of the formal written consent will be given to the participant.

Where the participant is ineligible, this, together with the reasons for ineligibility, will be documented by the clinical team member in the participant's medical notes (where applicable) or in the study file.

Participant's journey from the point of identification to the recruitment into the study (control group):

The control group participants will be recruited from the general public. The study recruitment posters will be displayed in the public areas such as waiting areas, canteens and cafes in University College London Hospitals (NHS Foundation Trust) or by advertising the study and/or displaying study posters in community hearing aid centres, AgeUK, the University of Third Age, and through the BRC BioResource Bank at UCLH and dedicated Facebook/social network and online groups.

The advertisement/study poster will contain contact details of the research student. Potential participants interested in the study will be able to contact the research student and will be provided with a participant information sheet together with an invitation letter upon contact. There will be no time limit to the participants' decision to take part in the study. If willing to participate, the potential participant will contact the research student and will be invited to attend University College London Hospitals (NHS Foundation Trust) or the UCL Ear Institute. The research student and the potential participant will agree on a suitable appointment day and time. The research student will ask the potential participant if willing to complete self-report questionnaires and if so, these will be sent out to the potential participant to complete at home (as a time-saving measure). These will not be collected until the appointment and only after the written consent has been obtained by the participant to take part in the study.

During the visit to University College London Hospitals (NHS Foundation Trust) or the UCL Ear Institute, the participant's questions pertaining to the study will be answered by the research student. The candidate's eligibility to participate in the study will be determined at this point, and the formal written consent to participate in the study will be obtained. The questionnaires that have been sent out to the participant will be collected at this stage and only after obtaining the formal written consent from the participant to take part in the study. No study related procedures will be performed without the participant's consent. The participant's decision to take part in the study will be documented in the study file. A copy of the formal written consent will be given to the participant.

Where the participant is ineligible, this, together with the reasons for ineligibility, will be noted and documented in the study file.

7.3.1 Consent

All research participants will be informed about the nature of the study in full. Formal written consent will be sought from each participant before proceeding with any study assessments.

All participants will receive a patient information sheet prior to their (first) visit and will have the opportunity to read through it before consenting to their participation in the study. The minimum time-interval of 24 hours will be given between when the participant information sheet is provided to the participant and their initial appointment with the research student.

The information provided in the patient information sheet will be discussed between the potential participant and the research student during the (first) study visit. The potential participant will be fully informed of the nature and purpose of the study and what his or her participation in the study will entail. The research student will discuss with the potential participant the tests and assessments that will be carried out in the course of the study as well as the potential implications of their findings. Any questions arising from the information given to the potential participant will be addressed by the research student then. If still willing to participate, formal written informed consent will be obtained from the potential participant. There will be no time limit to the participants' decision to take part in the study. Where there are doubts that the potential participant has the capacity to consent, the research student will assess this capacity. Where the participant does not have the capacity to consent, the consultation will be discontinued and the potential participant will not be able to take part in the research study. Where the participant who has given consent and is noted to have lost the capacity to consent during the study, his/her participation in the study will be stopped and such participant will be withdrawn from the research study. Identifiable data or tissue already collected with the consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.

The potential participants for this study are likely to have difficulty with hearing. The information will be presented to the potential participants in written and verbal format. Where the participant has a hearing impairment, the communication between the research student and the (potential) participant will be in written format as an alternative means of communication. If the alternative means of communication is inadequate, the research student will arrange for a designated sign-language translator to be present during the study appointments.
Participants who have a poor command of the English language will be offered to have a translator present for the consent and during each visit while participating in the study. This will be discussed

and arranged in advance by the research student. Where audiological tests require a good command of the English language, such tests will be omitted from the testing battery for the participants with a poor command of the English language.

8. ETHICAL AND REGULATORY COMPLIANCE

The final draft of the study protocol will be reviewed and approved by the Chief Investigator, the study co-investigators and the research student as well as the academic sponsor and will be in line with each site-specific regulation.

The study is conducted as part of a UCL(H) Biomedical Research Centre (BRC) Doctor of Philosophy (PhD) studentship and is funded by the UCL(H) BRC (Grant number BRC-1215-20016-546624). Additional funding for the study was obtained from Bernice Bibby Research Trust (Registered Charity Number 1058703). The Chief Investigator declares that otherwise no potential conflict of interest exists with regards to this study.

Benefits of participation in the study:

Participants may benefit from having their ears (all participants), hearing (all participants), balance and smell functions (siderosis group participants) tested in the clinical and study setting and with dedicated tests and questionnaires. These assessments may detect problems with participants' hearing (any group participants), balance and/or smell function (siderosis group participants) which they may not have known about. If hearing impairment is identified in the course of the study, the additional benefit incurred from participating in the study is the referral to the Adult Audiological Services at University College London Hospitals (NHS Trust) for further assessments and hearing impairment management, as appropriate. Furthermore, if clinically indicated, participants who may be referred to Ear, Nose and Throat (ENT) or Audio-vestibular Medicine (AVM) Services at University College London Hospitals (NHS Foundation Trust) for further assessments and management. In addition, any potential candidates for a cochlear implant will be referred to the Cochlear Implant Services at University College London Hospitals (NHS Foundation Trust) for further evaluation and management. The participant's primary healthcare team/General Practitioner will be notified of the relevant findings and alternatively, the referral may be made to a local team. This will be done with the prior consent to do so obtained from the participant.

A copy of the results of the assessments will be given to the participants and participants' healthcare team/General Practitioner, and/or the participant's next-of-kin, with the prior consent to do so obtained from the participant.

The assessments performed in the course of the study, however, may also identify findings of clinical significance that would not have been anticipated by the research team or the participant. All participants will be informed of such possibility prior to their decision to participate in the study. Each participant will be asked if they would like to be made aware of any significant clinical findings identified in the course of the study and whether they would like their primary healthcare team/General Practitioner to be notified of the findings so that the referral to appropriate services

can be made. The participant's decision will be documented in the participants' medical notes and study file during the initial consultation and ahead of any testing taking place. Should the participant not wish to be made aware of any significant findings during the study, the research student will enquire and ask permission to notify his/hers next of kin and/or the primary care team/GP. Neither the siderosis group participants who consent to saliva sampling and DNA testing nor their primary care teams/GP will be notified of the genetic testing results, neither during the study nor as part of other/future studies.

If required, counselling and explanation of the results and further management plan will be discussed with the participant. If a significant or unexpected clinical finding is detected or confirmed in the course of this study, the student researcher will convey their results to the participant's health-care team and/or further referral to the specialist services will be made.

Reimbursements and financial benefits of participation in the study:

For all group participants living in London/Greater London area, we will provide a flat fee of £15 (per visit) towards travel expenses (without receipts) and refreshments. For all group participants outside of London, we will reimburse their standard class tickets (subject to receipts) and will provide a flat fee of £15 (per visit) towards their travel expenses in London and refreshments when attending our research facilities.

Siderosis group (potential) participants will attend their Neuro-otology clinic appointments. The Neuro-otology clinic appointments will be arranged by the clinical team. The siderosis group participants or potential participants willing to take part in the study will be seen by the research student immediately after the clinic appointment. The potential participant's suitability for the study will be checked then and formal informed consent will be obtained. The research visit will be arranged by the research student for the date/time that is suitable for the participant and the research student.

For non-siderosis group participants the suitable visit dates and times to schedule the study visits will be discussed in advance by the research student and the potential participant. The visits will be arranged so that not to lead to the participant's any demonstrable loss of earnings, financial sacrifice, nor should impact their provision of care to another person (child-care; disabled-person care, older adult care).

No payments will be offered to the participants for their participation in the study. Should such decision (to offer payments to the participants for their involvement in the study) be made after the REC approval, this will be notified to the REC as a substantial amendment and implemented only after the REC approval is granted.

The description of reimbursements to participants in the study will be available and fully described in the Participant information Sheet.

8.1 Assessment and management of risk

Risks and burdens of participation in the study:

Participants in this research study will have minimal risk of harm or burden, as the assessments that the participants will undergo in the course of this study are already in the current clinical practice in the NHS and these are associated with minimal risk of adverse events.

The minimal risks that may arise from participating in this study include: (a) risk of minimal discomfort from undergoing the battery of tests and assessments as part of this study (b) risk of possible misunderstanding between the participant and the student researcher, (c) risk of breach of confidentiality, (d) risk of possible mishandling of participants' personal data.

(a) The clinical, audiological, vestibular assessments may be perceived as uncomfortable by the participants, yet these assessments constitute the standard current clinical practice within the NHS. Should the participant express their wish not to continue with any of the assessments or with further participation in the study, the assessment or the participant's involvement in the study will be terminated with no further repercussions to the participant's provision of clinical care or clinical follow-up, and data not obtained as a result of this will be recorded as missing.
(b) To minimise the possibility of a misunderstanding between the participants and the research student, the participants and their next-of-kin will be encouraged to ask questions and seek clarification at any point in the course of their participation in the study.
(c) The risks of breach of confidentiality or (d) possible mishandling of the participants' personal data will be further minimised by securely keeping the potential participants' contact details in a locked folder at University College London Hospitals (NHS Foundation Trust). Only the Chief Investigator and designated clinical team members will have access to the contact details of the potential participants. Once recruited onto the study, the participants' contact details (including personal addresses, postcodes, e-mail and telephone numbers) will then be entered by the research student and stored on the UCL secure safe haven data platform. The creation of coded, depersonalised data where the participant's identifying information will be replaced by an unrelated sequence of characters will be in place. No participant personal or identifiable data will be kept by the research student. The Chief Investigator, the research student and the academic supervisors/key protocol contributors will undergo General Data Protection Regulations (GDPR) and Data Protection Act (DPA) 2018 online training course before undertaking the study.

Recording and reporting of events and incidents:

Definition of adverse events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or study participant, which does not necessarily have a causal relationship with the procedure involved.
Serious Adverse Event (SAE).	Any adverse event that: • results in death, • is life-threatening*, • requires hospitalisation or prolongation of existing hospitalisation**, • results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect
*A life- threatening event, this refers to an event in which the participant was at 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. ** Hospitalisation is defined as an in-patient admission, regardless of length of stay. Hospitalisation for pre-existing conditions, including elective procedures do not constitute an SAE.	

Assessments of adverse events

Each adverse event will be assessed for severity, causality, seriousness and expectedness.

Severity (generic categories)

Category	Definition
Mild	The adverse event does not interfere with the participant's daily routine, and does not require further procedure; it causes slight discomfort

Moderate	The adverse event interferes with some aspects of the participant's routine, or requires further procedure, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

Causality and expectedness

Participants of this research study will have minimal risk of harm associated with their involvement in the study, as the study assessments are in the current clinical practice in the NHS and are known to be associated with no or minimal risk of adverse events.

This is an observational study and the need to capture the events related to the product application/medicinal product or medical devices procedure is not necessary for this study. The identifying causality or expectedness of adverse events is not necessary for this study.

Recording of adverse events

All adverse events will be recorded in the medical records in the first instance, and will include clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate. Any adverse event will be dealt with in accordance with the local hospital policies and protocols. The sponsor will be notified of any such untoward incidents in accordance with the sponsor's current protocol.

Procedures for recording and reporting of Serious Adverse Events

All adverse events that may occur while on site and during the participation in the study, will be recorded in the participant's medical records in the first instance, and will include clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate. Any adverse event will be dealt with in accordance with the local hospital policies and protocols. The sponsor will be notified of any such untoward incidents in accordance with the sponsor's current protocol. Completed forms for unexpected SAES must be sent within 5 working days of becoming aware of the event to the Sponsor.

Reporting of urgent safety measures

If any urgent safety measures are taken, the Chief Investigator shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC and Sponsor of the measures taken and the circumstances giving rise to those measures.

Reporting incidents involving a medical device

Because this is an observational study and does not involve trialling of a new medical device, and the assessments included in this study constitute standard clinical practice and are currently performed in the NHS, the need to capture the events related to the use of a new medical device is not applicable to this study. If there is a failure of clinical equipment used on site (University College London Hospitals NHS Foundation Trust), local reporting protocol and procedures will be followed.

Trust incidents and near misses

An incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

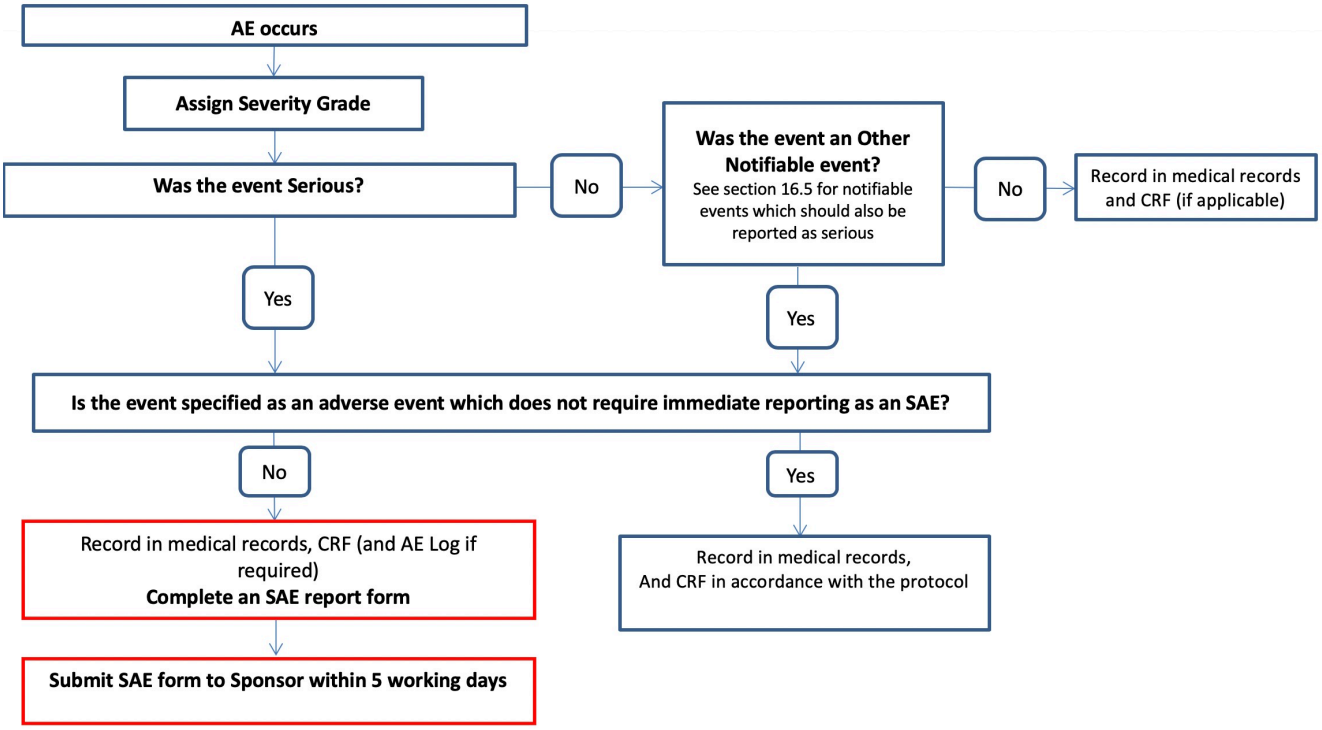
a) It is an accident or other incident which results in injury or ill health.
b) It is contrary to specified or expected standard of patient care or service.
c) It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d) It puts the Trust in an adverse position with potential loss of reputation.
e) It puts Trust property or assets in an adverse position or at risk.

A reportable incident is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a) It is an accident or other incident which results in injury or ill health.
b) It is contrary to specified or expected standard of patient care or service.
c) It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d) It puts the Trust in an adverse position with potential loss of reputation.
e) It puts Trust property or assets in an adverse position or at risk of loss or damage.

Incidents and near misses will be reported to the Trust through DATIX as soon as the individual becomes aware of them.

Flow Chart for SAE reporting



8.2 Research Ethics Committee (REC) and other Regulatory review & reports

Before the start of the study, a favourable opinion will be sought from the UK Health Departments Research Ethics Service NHS REC and HRA for the study protocol, informed consent forms and other relevant documents. The Chief Investigator will produce the annual reports as required and will notify the REC of the end of the study. Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

Regulatory Review & Compliance

The Chief Investigator will ensure that appropriate approvals from participating organizations are in place before any enrolment of participants onto the study takes place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance.

Amendments

Chief investigator will be responsible for the decision to amend the protocol and for deciding whether an amendment is substantial or non-substantial. The change will be submitted to REC and notified R&D office and local research team. The amendment history will be tracked to identify the most recent protocol version by protocol version and date listed. All amendment history will be recorded.

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

Protocol deviations and notification of protocol violations

A deviation is usually an unintended departure from the expected conduct of the study protocol/SOPs, which does not need to be reported to the sponsor. The Chief Investigator will monitor protocol deviations.

A protocol violation is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the study; or

(b) the scientific value of the study.

The Chief Investigator and sponsor will be notified immediately of any case where the above definition applies during the study conduct phase.

Monitoring and auditing

The Chief Investigator will ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol, procedures for consenting and ensuring that the data collected is of adequate quality.

The Chief Investigator will inform the sponsor should he/she have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures. UCL data monitoring /protection approval will be in place at the time of submission of the Ethics Proposal for this project.

Training

The chief investigator will review and provide assurances of the training and experience of all staff working on this study, including GCP and relevant clinical training to carry out the clinical assessments and procedures as per protocol. Appropriate training records will be maintained in the study files. All researchers in this project are working clinicians with appropriate prior training and qualification for the tasks. None to very minimal further specific training is needed since all procedures are routine clinical tests/assessments which are used daily in the clinical setting. However, meeting of all researchers prior to the start of the project will be done to ensure understanding of the uniform steps and participants flow.

Intellectual property

All intellectual property rights and know-how in the protocol and in the results arising directly from the study, but excluding all improvements thereto or clinical procedures developed or used by each participating site, shall belong to UCL. Each participating site agrees that by giving approval to conduct the study at its respective site, it is also agreeing to effectively assign all such intellectual property rights ("IPR") to UCL and to disclose all such know-how to UCL, with the understanding that they may use know-know gained during the study in the provision of clinical services and teaching to the extent that such use does not result in disclosure of UCL confidential information or infringement of UCL IPR.

8.3 Peer review

The study has been peer reviewed in accordance with the requirements outlined by UCL. The Sponsor considers the procedure for obtaining funding from the NIHR UCL(H) Biomedical Research Centre to be of sufficient rigour and independence to be considered an adequate peer review.

8.4 Patient & Public Involvement

Prior to Ethics application, the opinion of several members of the public was sought regarding the content of recruitment leaflet and the study poster. Opinion and involvement of patients and members of public will also be sought during various stages of the study, regarding (1) the optimal number of appointments, their duration, timings and number of tests included during each appointment); (2) communications needs and how to best address them if arise, as well as the optimal way of communication (phone or email). Furthermore, (3) suggestions and opinion regarding the dissemination of the study results will be sought from the public.
In addition, infratentorial superficial siderosis support groups will be contacted online to provide suggestions and feedback on the study methodology and dissemination of the results.

8.5 Protocol compliance

The protocol compliance will be monitored by the Chief Investigator. Any protocol deviations will be adequately documented and reported to the Chief Investigator and sponsor immediately. When protocol deviation frequently recurs, appropriate investigation and intervention from the Chief Investigator will be immediately put in place.

8.6 Data protection and patient confidentiality

All investigators and the study site staff will comply with the requirements of the General Data Protection Regulation (GDPR) and Data Protection Act (DPA) 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. The chief investigator, the student researcher and the academic supervisors will undergo online GDPR training course before undertaking the study.

A member of the respective clinical team will have access to the potential participants' personal information as part of their clinical care. The designated member of the clinical team will ask the potential participant for permission to be contacted by the research student to provide information regarding the study. If such permission is given, the clinical team member will provide contact details to the research student to contact the potential participant and send the Participant Information Sheet together with an invitation letter and a pre-paid self-addressed envelope. Age-related hearing loss group potential participants (who are recruited from the general public) and control group potential participants who express their interest in participating in the study will contact the research student and will be provided with a Participant Information Sheet together with an invitation letter upon contact. The participants' contact details (including personal addresses, postcodes, e-mail and telephone numbers) will then be entered by the research student and stored on the UCL secure safe haven data platform for the duration of the study (three years).

The creation of coded, depersonalised data where the participant's identifying information is replaced by an unrelated sequence of characters will be in place. The digital data collected by the research student in the course of the study will be stored in digital format in UCL secure safe haven data platform with encrypted and password protection.
The data (hard copies) collected during the study will be stored in the study site file at University College London Hospitals NHS Foundation Trust - for participants who underwent their testing in University College London Hospitals (NHS Foundation Trust) or at the UCL Ear Institute - for participants who underwent their testing in the UCL Ear Institute. The study site files will be stored in a securely locked designated cabinet at University College London Hospitals (NHS Foundation Trust) (for the participants tested at the UCLH NHS Foundation Trust) or at the UCL Ear Institute (for participants tested at the UCL Ear Institute) for the duration of the study (three years). Only the Chief Investigator, the research student and the designated clinical team members will have access to the electronic file with the participants' contacts and to the file containing de-identified

study digital data. Secure maintenance of the data and the linking code in separate locations within lock folders and storage media will be ensured.
The full data set will only be accessed by the Chief Investigator for quality control, audit, and analysis. The confidentiality of the electronic data will be preserved by encrypted digital files within a password protected folder when the data are transmitted to sponsors and co-investigators.
In accordance with the UCL Records Retention Policy, the anonymised research data collected in the course of the study are retained by UCL in their capacity as a sponsor for 20 years after the research study has ended. The data are then securely destroyed.

Access to the final study dataset

The Chief Investigator, the study co-investigators (academic supervisors) act as a steering group and will have access to the full dataset in order to ensure that the overall results are not disclosed by an individual study site prior to the main publication.
The study will allow site investigators to access the full dataset if a formal request describing their plans is approved by the steering group.
The full dataset can be used for secondary analysis. This can only be undertaken with the prior consent of the participants. The information about the future use of these data in research is fully explained in the participant information sheet and consent form.
UCL and each participating site recognise that there is an obligation to archive study-related documents at the end of the study (as such end is defined within this protocol). The Chief Investigator confirms that he/she will archive the study site files at University College London and at University College London Hospitals (NHS Foundation Trust) for the period stipulated in the protocol and in line with all relevant legal and statutory requirements. The Chief Investigator agrees to archive the site's study documents at both participating sites for the period stipulated in the protocol and in line with all relevant legal and statutory requirements.

8.7 Indemnity

The study has a minimal to no potential risk. The study involves performing clinical examination as well as the assessment of hearing, balance and smell functions, and peripheral venous blood sampling, as described above, all of which are standard clinical procedures performed in in the NHS. Imaging and cognitive assessments will be performed in line with the clinical care pathway and will be arranged by the clinical team. It will not formally constitute an assessment as part of this study.

University College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that University College London has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital's duty of care or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

9. DISSEMINATION POLICY

9.1 Dissemination policy

On completion of the study, the data from the anonymised dataset collected in the course of the study will be analysed and tabulated and a Final Study Report prepared by the Chief Investigator along with guidance from the study co-investigators. The selected data will be used for the research student doctoral thesis and will be submitted to University College London. Further manuscripts derived from the data will be published in academic journals. Dissemination of the study results in the relevant clinical/scientific peer-reviewed literature and at relevant meetings and conferences will take place upon the study completion. No participant identifiable data will be included in the final study reports or in the process of dissemination of the study results, as described above.

The participants will be guided to where they can access the final result publication(s). It is possible for the participant to specifically request results from their chief investigator after the results had been published. The study protocol and study report will be published. The anonymised participant level dataset and statistical code for generating the results will not be publicly available.

9.2 Authorship eligibility guidelines and any intended use of professional writers

The Chief Investigator, the study co-investigators (academic supervisors) and the student researcher will gain authorship in the final study report.

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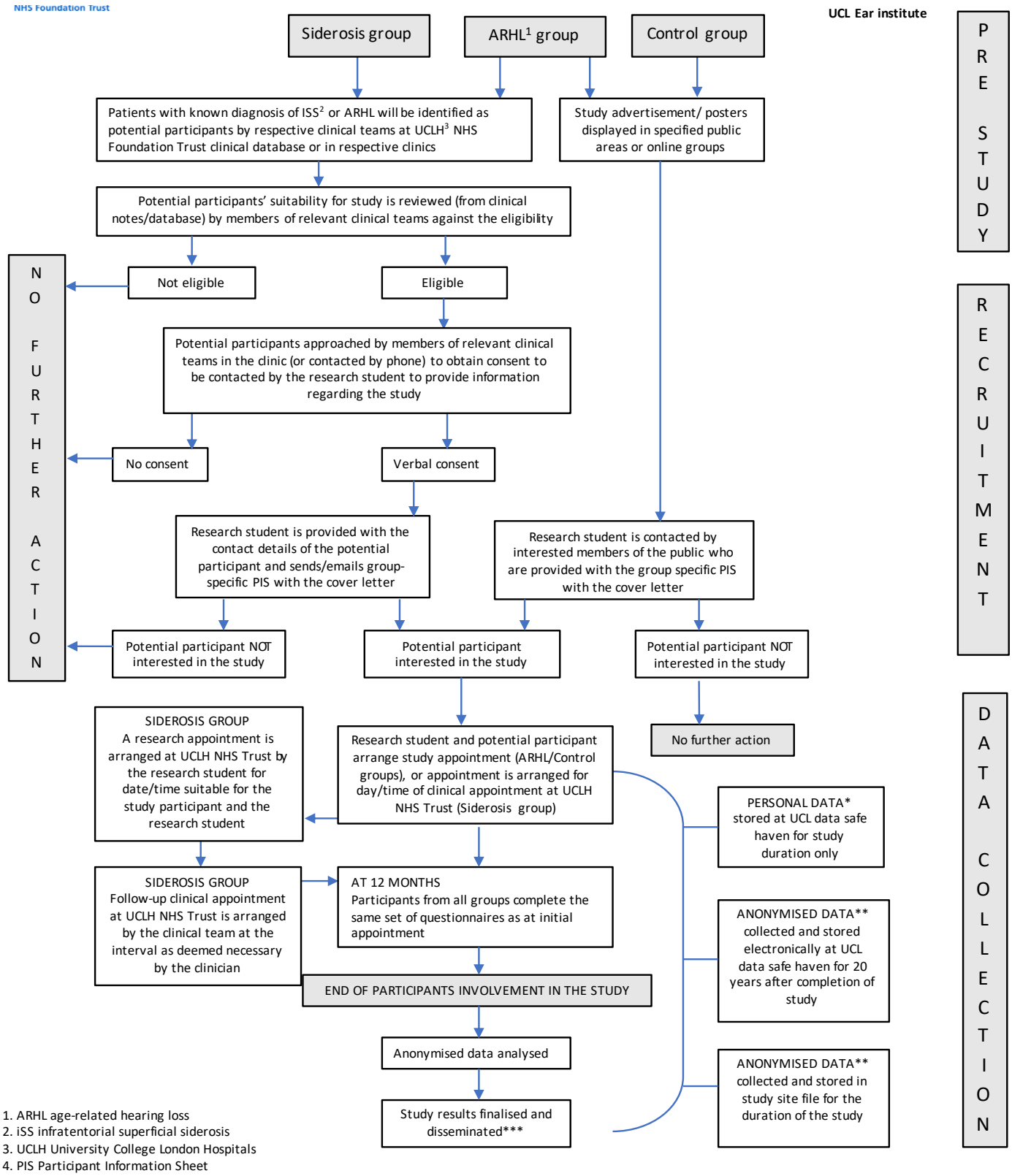
11. APPENDICES

11.1 Appendix 1

Study Participant Recruitment and Data Collection Flow Chart



1. ARHL age-related hearing loss
2. iSS infratentorial superficial siderosis
3. UCLH University College London Hospitals
4. PIS Participant Information Sheet

* Personal data (participants name and contact details) for all study participants will be stored on secure UCL data safe haven platform for the study duration only
** Anonymised data will be stored electronically at UCL data safe haven and in the site file in secure locked cabinet in UCLH (for participants who underwent their assessments in UCLH NHS Trust), and in the site file in secure locked cabinet in UCL (for participants who underwent their assessments in UCL)
***Participants will be advised to contact the research student to obtain final results of the study

11.2 Appendix 2 – Schedule of Procedures

Procedures	VISITS/TIME-POINTS				
	All groups		Siderosis Group		All groups
	Visit/time-point 1		Visit/ time-point 2	Visit/ time-point 3	12-month follow-up
	Clinical	Research	Research	Clinical	Research
Informed consent	SG	X	SG		
Clinical/neuro-otological assessment, including medical history and physical examination (as per protocol)	SG	X	SG		
Hearing tests: – Pure tone audiometry – Screening tympanometry – Speech-in-quiet – Acoustic reflex thresholds – Auditory brainstem response – Speech-in-noise testing	SG SG - - SG -	X X X X X X	- - SG SG - SG		
Hearing questionnaires *- Modified Amsterdam Inventory for Auditory - Disability and Handicap (mAIADH)* *- Speech, Spatial and Qualities of Hearing Scale* *- Tinnitus Functional Index*		X	SG	SG	ALL*
Quality-of-life questionnaires *-Health Utilities Index-3* *-EuroQoL Questionnaire* *- Evaluation of the Impact of Hearing Loss in Adults (ERSA)*		X	SG	SG	ALL*
Balance (vestibular) tests: – Vestibular nystagmography – Vestibular evoked myogenic potentials – Video head impulse test – Functional gait assessment – Scale for assessment and rating of ataxia	SG - SG - -		SG - - SG SG	- SG - - -	
Balance (vestibular) questionnaires *- Dizziness Handicap Inventory* *- Situational Vertigo Questionnaire*			SG	SG	
Smell (olfactory) assessment			SG		
Saliva sampling for DNA banking			SG		

*These will be sent out and collected by post or electronically
X = Participants from ARHL/Control groups
SG = Participants from Siderosis group only
ALL = Participants from all groups
ARHL = age-related hearing loss group