A Combined Laryngeal and Respiratory Approach to Presbyphonia Voice Therapy: Phase One

CLEARER - Phase One

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Version 5, 15th May 2025

R&D / Sponsor Reference Number(s): 166991

PROTOCOL VERSIONS

Version Stage	Versions No	Version Date	Protocol updated & finalised by;	Appendix No detail the reason(s) for the protocol update
Current	5.0	15th May 2025	Brian Saccente-Kennedy	Change to statistical methods to include historical control data and no stratification by sex.
	4.0	27th February 2025	Brian Saccente-Kennedy	Extension of study end date.
	3.0	16th December 2024	Brian Saccente-Kennedy	Addition of two sites – Whittington Hospital and Charing Cross Hospital
	2.0	12th August 2024	Brian Saccente-Kennedy	Following REC requests for clarity of the definition of the end of the study.
	1.0	18 July 2024	Brian Saccente-Kennedy	

DECLARATIONS

The undersigned confirm that the following protocol has been agreed and accepted and that the investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the Research Governance Framework 2005 (as amended thereafter), the Trust Data & Information policy, Sponsor and other relevant SOPs and applicable Trust policies and legal frameworks.

I (investigator) agree to ensure that the confidential information contained in this document will not be used for any other purposes other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I (investigator) also confirm that an honest accurate and transparent account of the study will be given; and that any deviations from the study as planned in this protocol will be explained and reported accordingly.

Chief Investigator:

Signature:  **. Date 18/07/2024.**

Print Name (in full): Brian Saccente-Kennedy

Position: NIHR Doctoral Clinical and Practitioner Academic Fellow

On behalf of the Study Sponsor:

Signature:  **Date: 18/ 07/2024**

Print Name (in full): PUSHPSEN JOSHI

Position: RM&G UCL/UCLH JRO

STUDY SUMMARY

Identifiers	
IRAS Number	328486
REC Reference No	24/PR/0948
Sponsor Reference No	166991
Other research reference number(s) (if applicable)	LNWUH R&D: RD23/041
ISRCTN Registration	ISRCTN34699816
Full (Scientific) title	A Combined Laryngeal and Respiratory Approach to Presbyphonia Voice Therapy: Phase One
Health condition(s) or problem(s) studied	Presbyphonia (age-related voice disorder)
Study Type i.e. Cohort etc	Cross-sectional
Target sample size	35
STUDY TIMELINES	
Study Duration/length	10 months
Expected Start Date	1st September 2024
End of Study definition and anticipated date	The date of the visit of the final study participant (Anticipated 30th June 2025)
Key Study milestones	Submission to HRA/REC, first patient recruited, last patient recruited.
FUNDING & Other	
Funding	NIHR Academy (NIHR303555)
Other support	None
STORAGE of SAMPLES (if applicable)	
Data collected / Storage	Data to be stored internally.
KEY STUDY CONTACTS	Full contact details including phone, email and fax numbers
Chief Investigator	Brian Saccente-Kennedy 07872 863 442 brian.saccente-kennedy@nhs.net
Lead Statistician	Dr Martin Wiegand Department of Statistical Science University College London m.wiegand@ucl.ac.uk +44 20 3108 5580

KEY ROLES AND RESPONSIBILITIES

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 Chief Investigator 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.

LEAD STATISTICIAN: The statistician is the person who takes responsibility for the determination of sample size, the selection of statistical methods and the design of a statistical analysis plan for the study, offering some independent advice and conclusions around any difference between the study population and published normative data.

KEY WORDS

presbyphonia, age-related dysphonia, speech-breathing, respiration, respiratory kinematics, spirometry.

LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
ENT	Ear, Nose and Throat
GAfREC	Governance Arrangement for NHS Research Ethics
HTA	Human Tissue Authority
IB	Investigator Brochure
ICF	Informed Consent Form
MD	Medical Device
ISRCTN	International Standard Randomised Controlled Studies Number
PI	Principle Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Clinical Study
REC	Research Ethics committee
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SDV	Source Data Verification
SLT	Speech and Language Therapist/Therapy
SOP	Standard Operating Procedure
SSI	Site Specific Information
TMF	Trial Master File

CONTENTS

1 INTRODUCTION

Voice disorders, called dysphonia, affect 7.5% of the population,[1,2] impairing mental health, social functioning and the ability to work similar to chronic health conditions like congestive heart failure.[3] The prevalence of dysphonia in adults over the age of 65 is 20-30%,[4–6] 3-4 × that of the general population. For those in care homes, it is 40%.[7] Voice clinic referrals for older people already outpace their proportion in the population, comprising >20% of dysphonia diagnoses.[8,9] When prevalence is considered, the costs associated with treating dysphonia are comparable to COPD and asthma.[10]

Dysphonia due to age-related changes to the larynx and respiratory system, called *presbyphonia,* is the most common form of dysphonia for over-65s.[8,11] It disproportionally impacts the daily lives of older people, with 50% experiencing a significantly reduced quality of life.[6] It impairs participation in communities, engenders low mood and can result in social isolation[5,12,13] – a known risk factor for infectious disease, dementia and mortality.[14–16] Also, as up to 35% of older people with presbyphonia are still in employment and require a healthy voice for work,[9,17] there are additional implications both for individual financial security and the nation's economy through sickness-related costs.

The mainstay for presbyphonia treatment is voice therapy with a Speech and Language Therapist (SLT).[18] Research into presbyphonia and its treatment with voice therapy has previously focused on age-related laryngeal atrophy with comparatively little attention paid to the equally important role of age-related changes to respiration. This cross-sectional observational study is the first phase of a multiphase project aiming to address this gap in our knowledge of the disorder and its treatment by developing a combined laryngeal and respiratory-focused treatment for presbyphonia.

The present study seeks to characterise the respiratory presentation and speech-related breathing patterns of people with presbyphonia and identify how these correlate with the subjective experience of vocal handicap. This primary research will inform both treatment design and physiologically based treatment targets for latter phases of the project, culminating in a multi-centre feasibility trial of the new treatment.

2 BACKGROUND AND RATIONALE

The respiratory system is the power source of the voice, supplying air pressure and airflow to the vibrational source - the larynx. As the larynx and the lungs are mechanically coupled, changes in one system affect the other - both are required for healthy voice.[19,20] The literature on presbyphonia, however, has focused on laryngeal atrophy and paid scant attention to the role of ageing respiration, marking this as a significant gap in our knowledge of presbyphonia and potential treatment options. [21–23] In our recently published systematic review of SLT interventions for presbyphonia,[24] respiratory measures were the least reported category of outcomes, investigated by only 4 of the 23 included studies.

There is mounting evidence that laryngeal atrophy is insufficient to fully explain presbyphonia; it does not reliably predict the occurrence of presbyphonia, nor is it correlated

to the experience of vocal handicap for those diagnosed with it.[22,23,25] In fact, Crawley and colleagues identified that laryngeal atrophy was as commonly found in elderly treatment-seeking voice patients as in their age-matched normative peers.[26] In another study, the degree of muscle wasting in the larynx was not correlated to the individual experience of vocal impairment.[27]

Sarcopenia, the process of age-related muscle loss which drives laryngeal atrophy, also affects the muscles of the thorax and of respiration. This begins by the age of 50,[28] and together with kyphosis and reductions in intrathoracic volume, produces an exponentially smaller respiratory vital capacity from the age of 65.[29] Additionally, changes to the connective tissue of the lungs results in reduced elasticity and recoil pressures in expiration.[30]

Speech breathing patterns, the coordination of inspiratory and expiratory forces to maintain airflow and pressure for speech, are known to differ between young people and older people.[20,31–33] As a result of age-related change, older people breathe and initiate speech at a higher lung volumes to capitalise on higher recoil pressures, and thus compensate for age-related loss of efficiencies in the system.[30–32] It has also been demonstrated that they have a more difficult time coping when the speech system is taxed by utterance length and loudness.[32]

The speech breathing patterns utilised by people with presbyphonia, however, have not yet been described and little is known about how they contribute to the pathogenesis of the disorder. That speech breathing contributes to voice impairment has support in the literature as it is known to differ between age-matched subjects with and without voice disorders.[34,35] Given the interplay between respiratory and laryngeal systems in presbyphonia, speech breathing in this pathological population is hypothesised to be divergent from norms and most likely inefficient. Such differences may explain why some older adults cope well with age-related decline and others develop symptomatic presbyphonia.

This cross-sectional observational study is the first phase of a multiphase project to design and test the feasibility of a novel combined laryngeal and respiratory-focused treatment for presbyphonia. In seeking to uncover the speech breathing patterns of patients with presbyphonia and correlate these with spirometry, laryngeal appearance, voice quality, laryngeal aerodynamics and the subjective experience of vocal handicap, we hope to elucidate the pathophysiology of presbyphonia and identify physiologically based treatment targets to inform treatment design in the next phase of the project.

3 OBJECTIVES

3.1 Primary Objective

To characterise the speech breathing patterns of people over 50 years of age with presbyphonia.

3.2 Secondary Objectives

To identify any correlations between speech breathing metrics and laryngeal appearance, lung function, respiratory muscle strength, self-reported vocal handicap, acoustic voice metrics and perceptual voice quality.

To compare the speech breathing patterns of people over 50 years of age with presbyphonia against published data for a normative age-matched peers without presbyphonia.

4 STUDY DESIGN

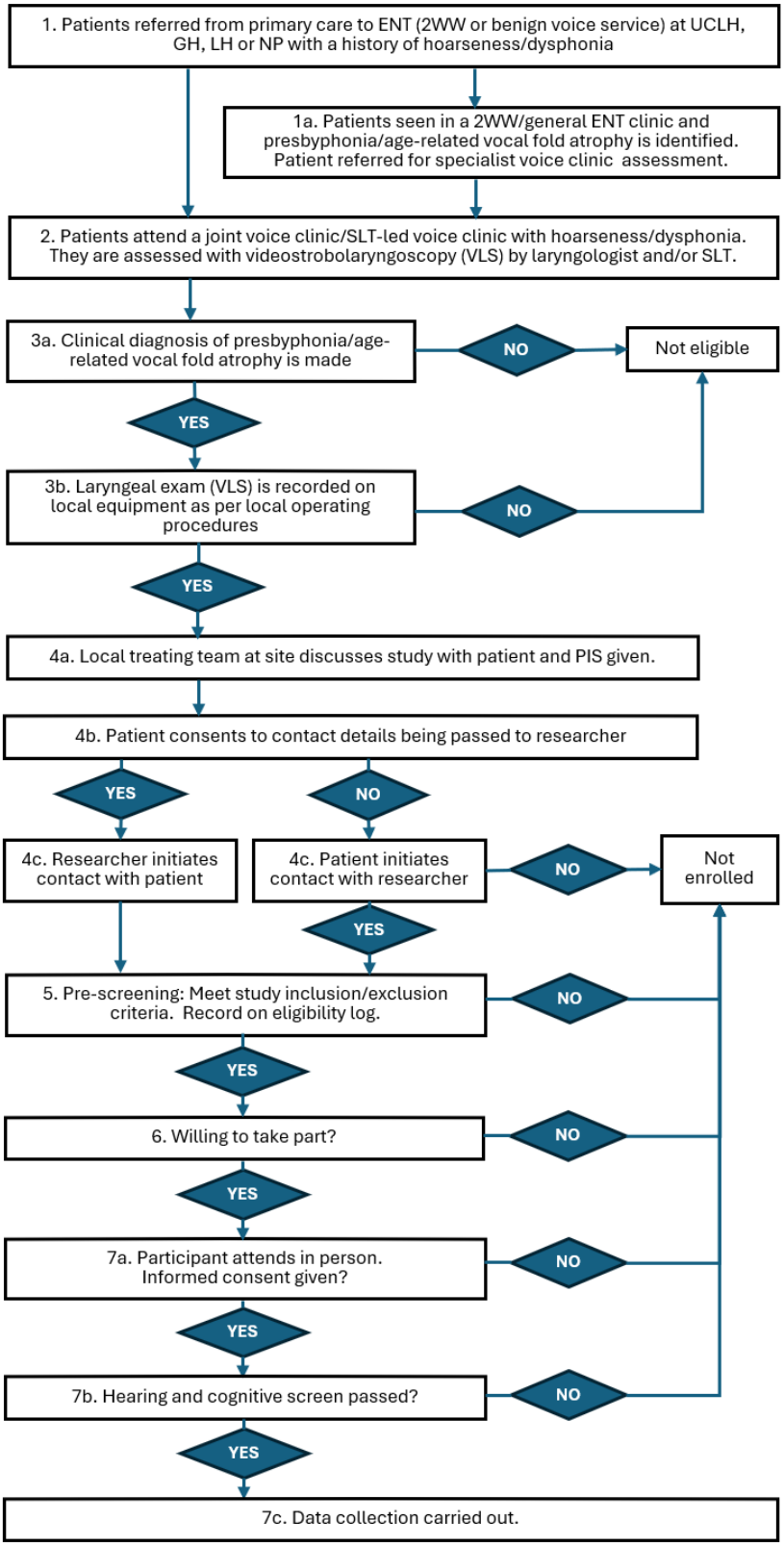
This is a cross-sectional study of the speech breathing and respiratory behaviours of patients diagnosed with presbyphonia. Thirty-five people over the age of 50 with presbyphonia will be identified from ENT services at four research sites and recruited to attend a single research visit for data collection which will last approximately 1.5-2 hours. The study flow chart, overleaf, details this process from identification, to screening, recruitment, and data collection.

We will identify treatment-seeking patients from the voice and laryngology clinics at the Royal National ENT Hospital (RNENT), Guy's Hospital (GH), University Hospital Lewisham (UHL), Northwick Park Hospital (NPH), Whittington Hospital (WH) and Charing Cross Hospital (CXH). These six sites have been selected as they have highly specialist voice services, high-quality laryngoscopy and adequate referrals (audit data confirms ~30 presbyphonia referrals per annum per site). Recruiting from multiple sites across London also enables diverse recruitment from wider ethnic and socioeconomic backgrounds.[36]

We will test for a minimum clinically significant difference (6%) in the mean lung volume initiation (LVI) between our recruited cohort and those of historical controls[31] with a two-sided two-sample t-test. As speech breathing in presbyphonia has not yet been described, this figure allows for a more subtle difference than that identified in the literature for younger subjects with/without a voice disorder (~8%[34]). Assuming this minimum difference and a significance level of 0.05, a sample size of 14 men and 21 women will give sufficient power (0.8) in both groups.

5 STUDY SCHEDULE

Eligible participants will be approached by a member of the ENT or SLT teams at each site, who will provide a PIS and request consent for their contact details to be passed to the researcher to make contact (see Figure 1). If permission to contact the participant is given, the researcher will make contact to carry out a pre-screening via telephone; if permission to contact is not given, participants will be free to initiate contact with the research team, and a pre-screening telephone call will be arranged as and when such contact is made.



Participants will be pre-screened against initial eligibility criteria and entered into a recruitment log with a participant identifier. If they pass the initial screen, they will be invited to participate in a study visit at RNENT and informed that ultimate eligibility to proceed with

participation requires passing a hearing screen on the day. Participants will be given at least 24 hours to consider consenting to participate.

During this study visit at RNENT, informed written consent will be finalised in advance of undergoing a hearing and cognitive screen to ensure final eligibility. Data collection will then take place during a single session, approximately two hours long. At this session, participants will answer validated questionnaires and will undergo spirometry, respiratory muscle strength assessment, speech-breathing assessment and voice assessment (including acoustic and aerodynamic assessment). Participants can withdraw at any time during this session by verbally requesting this.

The study will end on the date of the study visit of the final participant (anticipated to be 10 months from opening for recruitment, 30th June 2025).

6 CONSENT

Participants who have been identified by their clinical teams as meeting inclusion criteria, have passed an initial pre-screening by the Chief Investigator and have confirmed desire to take part will be invited to a face-to-face research appointment. The Chief Investigator will undertake informed consent for all participants at the start of the research appointment, having explained the details of the study via the PIS during the initial pre-screening telephone call, ensuring the participant has sufficient time to consider participating in advance of informed consent being taken and ask any questions.

We will collect data including ethnicity, gender, disability and preferred spoken language during participant identification and screening. For participants who are non-English speakers, an interpreter can be made available for both the initial pre-screening call as well as on the day for consenting, hearing/cognitive screening and face-to-face data collection. Written study materials, themselves, will not be available in other languages owing to the wide variety of possible participant home languages.

Informed consent will be collected from each participant prior to hearing/cognitive screening and data collection. As consenting precedes cognitive screening, the participants' ability to give informed consent will be checked through an informal understanding check; participants will be given two opportunities to correctly explain back to the researcher the main components of consent (what the purpose of the study is, what they will be asked to do, what the possible risks and benefits are and that they understand they can quit at any time). One copy of a signed consent form will be given to the participant, one will be kept by the research team and a third will be sent to the participants' GP for inclusion in medical records.

7 ELIGIBILITY CRITERIA

7.1 Inclusion Criteria

- 50 years of age or older
- ENT consultant-confirmed diagnosis of presbyphonia
- Laryngeal images from most recent ENT exam available for analysis

- Typical hearing (as indicated by hearing screening at 40 dB HL at 500, 1000 and 1500Hz, bilaterally), wearing hearing aids (if applicable).
- Willing and able to offer informed consent

7.2 Exclusion Criteria

- Recent (<12 months) voice therapy
- Current diagnosis of a neurological condition affecting laryngeal or respiratory function (i.e. Parkinson's disease, CVA, spasmodic dysphonia)
- Current diagnosis of additional laryngeal pathology
- Contraindicated for spirometry
- Failing cognitive screen (scoring <23 on the *Rowland Universal Dementia Assessment Scale,* RUDAS)

8 RECRUITMENT

Participants will be identified by ENT and/or SLT clinicians at joint- or SLT-led voice clinics at the four research sites during routine appointments (see Figure 1) as having a diagnosis of presbyphonia without any other laryngeal pathology/neurological condition affecting laryngeal/respiratory function or diagnosed dementia. Clinicians will also ensure that laryngeal images are recorded as per local Trust procedures.

In most instances, participants will be approached by their clinician during their voice clinic appointment and will be given a verbal description of the study and a PIS. The clinician will seek the participant's permission for the research team to contact them by phone. In some instances (for example, if a patient with presbyphonia is on a waiting list for voice therapy prior to the opening of the study and is noted to meet the eligibility criteria after their clinic appointment), a treating clinician will send eligible patients a letter informing them of the study. The letter will explain that they may be eligible for a research project and will include a PIS. The letter will invite the patient to make contact and will state that the treating SLT will give them a courtesy call 1-2 weeks later to see if further information is wanted.

Participants will then be given the choice of either contacting the research team themselves, or their permission sought by their clinician to pass their names and contact details on to the researcher to contact them. When the participant initiates contact/the researcher initiates contact (dependent on whether contact details were passed on), an initial telephone pre-screening will be undertaken by the researcher to identify if the participant meets eligibility/exclusion criteria and if any interpretation is required for non-native English speakers. (Hearing and cognitive screening will not take place via initial telephone screening.) Outcome of initial screening to be recorded in a recruitment log. The researcher will confirm the participant's willingness to take part and book a date/time to come to RNENT for informed consenting, final screening and data collection.

On the day of data collection, the participant will be consented, and then will undergo hearing and cognitive screening. If either of these are not passed, the participant is withdrawn from the study and the outcome recorded on the recruitment log.

Data collection is carried out in a single, approximately 1.5-2-hour session. This will include the completion of questionnaires (the Aging Voice Index, the Cincinnati Dyspnea Questionnaire), spirometry, respiratory muscle strength assessment, speech-breathing assessment, aerodynamics assessment and the recording of voice samples for later analysis.

9 STATISTICAL METHODS

To investigate speech breathing and respiratory behaviour in people over 50 with presbyphonia, we choose a cross-sectional, observational study design.

9.1 Outcomes (also, see Appendix)

9.1.1 PRIMARY OUTCOMES

The primary outcome will be the mean lung volume initiation (LVI).

9.1.2 SECONDARY OUTCOMES

The secondary outcomes will be:

- **Additional speech breathing metrics** (lung volume termination (LVT), lung volume excursion (LVE), % vital capacity/syllable (%VC/syl), % ribcage contribution (%RC), speech rate (syllables/sec), utterance length, abdominal-ribcage coordination (laboured breathing index, LBI) and measures of forward planning (LVI/LVT vs utterance length))
- **Spirometry** (forced vital capacity (FVC), peak expiratory flow (PEF), forced volume in 1 second (FEV1), ratio of FEV1/FVC), respiratory muscle strength (maximum expiratory pressure (MEP), maximum inspiratory pressure (MIP))
- **Aerodynamics** (laryngeal resistance)
- **Voice quality measures** (Acoustic Voice Quality Index (AVQI), Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V)),
- **Patient-reported measures** (Aging Voice Index score (AVI), Cincinnati Dyspnoea Questionnaire, Effort level).

9.1.3 EXPLORATORY OUTCOMES

Laryngeal appearance/function (Bowing Index (BI), closure pattern, supraglottic activity).

9.2 SAMPLE SIZE AND RECRUITMENT

9.2.1 SAMPLE SIZE CALCULATION

The study is powered to test for a minimum clinically significant difference (6%) in the mean lung volume initiation (LVI) between our recruited cohort with presbyphonia and the means identified from historical control data for normal older adults[31] with a two-sided two-sample t-test. We apply the pooled standard deviation from previous publications[20,33] of 8.08%. Assuming a significance level of 0.05, a sample size of 35 recruited participants and 25 historical control participants will give us 80% power.

9.2.2 RECRUITMENT

We expect the recruitment to be completed within 10 months.

9.3 RANDOMISATION

No randomisation is planned, as the recruited patients will be a convenience sampling. We will only ensure that we reach sufficient numbers in an appropriate age range.

9.4 STATISTICAL ANALYSIS

9.4.1 Summary of baseline data and flow of participants

Summary measures for the baseline characteristics of each group will be presented as mean and standard deviation for continuous (approximate) normally distributed variables, medians and interquartile ranges for non-normally distributed variables, and frequencies and percentages for categorical variables. The impact of missing data and non-compliance will be investigated.

9.4.2 PRIMARY OUTCOME ANALYSIS

The primary outcome will be analysed by a two-sample, two-sided t-test for differences in means. We will compare the mean lung volume initiation (LVI) in both men and women between our recruited cohort and a historical control cohort.[31] All confidence intervals will be reported two-sided. All model assumptions will be checked.

9.4.3 SECONDARY OUTCOME ANALYSIS

The secondary outcome analysis will be analogous to the primary outcome analysis.

9.4.4 SENSITIVITY AND OTHER ANALYSES

We will investigate how secondary outcomes impact the primary outcome with a linear regression model. There will be a sensitivity analysis on how different age groups and sex impact the difference in the primary outcome.

9.5 OTHER STATISTICAL CONSIDERATIONS

Any additional or deviation(s) from the original statistical plan will be described and justified in the final report.

10 PATIENT AND PUBLIC INVOLVEMENT (PPI)

Patients have had a consistent voice from the conception through to the development of this project. 10 older patients with dysphonia (or their partners) were interviewed on their experience of living with their voice disorder, their desires for research, and on the acceptability of the proposed project. We proactively sought the input of individuals from diverse and minoritised groups; 40% of my participants were from a BAME background, 10% identified as LGBTQ, and a wide range of educational and socioeconomic backgrounds were also represented.

Patient partners identified some of the outcome measures of interest in this study (the need for expert-rated auditory-perceptual voice quality, age-appropriate voice-related quality of life measures, measures of discomfort) and their input helped to identify the number and location of research sites. They have also helped to produce the PIS, the consent form and other materials required for local and national approvals and to ensure barriers to inclusive participation are overcome.

As part of the wider, multiphase project to which this study belongs, a PPI group of six members will meet three times per year. They will be jointly involved in the production of dissemination materials regarding findings in the form of posters and pamphlets for GP surgeries and community centres.

11 FUNDING AND SUPPLY OF EQUIPMENT

The study funding has been reviewed by the UCL/UCLH Research Office and deemed sufficient to cover the requirements of the study. NHS costs will be supported via UCLH and/or the Local Clinical Research Network.

The research costs for the study have been supported by the NIHR Academy as part of a Doctoral Clinical and Practitioner Academic Fellowship (NIHR303555: £300,669. January 2024). This includes the costs associated with our sub-contracted Lead Statistician, Dr Martin Wiegand (UCL Department of Statistical Science)

The equipment that will be used in this study, namely a Respitrace inductive plethysmography unit, a Vitalograph Spirometer with respiratory muscle strength assessment, a PENTAX Phonatory Aerodynamics System, microphones, pre-amps and lab computer, are all owned by the Speech and Language Therapy (ENT) Team at the RNENT, the Chief Investigator's substantive employer. These will be used in the RNENT voice lab during data collection. Other small bits of equipment (encrypted hard-drives, laptop, etc) have been purchased as part of the above grant.

12 DATA HANDLING AND MANAGEMENT

Confidentiality of study participants will be upheld by the Chief Investigator. All data collection will adhere to the guidelines of the Data Protection Act 2018 and the General Data Protection Regulation (GDPR). Access to personally identifiable information will be limited to the Chief Investigator and only when necessary for communication with the participant.

Personal data, including basic personal information (such as name, contact number) will be collected by the identifying ENT/SLT clinician at the point of identifying potential participants and shared to the Chief Investigator via NHS.net email so that they can be contacted for pre-screening. Once informed consent is obtained during the study visit, participant contact details will be stored along with paper consent forms files in a locked cabinet at a secure location accessible only to the Chief Investigator. This will be in an area accessible with swipe card access and locked away in a cupboard. The participant's unique study identifier will be used for identification in study data, ensuring the separation of personal identification from research data.

Data collected during assessments, including sound recordings, inductive plethysmography traces, aerodynamic data and scanned questionnaires will be stored as raw files on an encrypted, password-protected device with the participant's unique identifier used to label the files. Details of data linking the participant to the code will be securely stored on UCLH servers, separate from pseudonymised data. All data to be analysed will be identified solely by the participant's unique identifier.

Laryngeal images/video recordings, retrieved with participant consent from their treating ENT/SLT team at their home NHS Trust, will be stored securely on an encrypted password-protected device. Such images/video recordings will be cropped, if necessary, to remove any identifiable data (i.e. name, hospital number) and the files will be identified only with the

participant's unique pseudonymised study identifier. Only the Chief Investigator will have access to the encrypted password-protected device storing the videos.

CRFs will only collect the minimum required information for the purposes of this study. CRFs and anonymised patient-reported data (questionnaires, effort level) will be recorded on fillable electronic forms and transferred to a master Excel spreadsheet for later analysis. Any original paper questionnaires will be held securely, in a locked room, or locked cupboard or cabinet. Access to this information will be limited to the Chief Investigator and relevant regulatory authorities.

Access to study data will be restricted to the research team. Publications arising from the study will maintain participant confidentiality. The Chief Investigator is responsible for data collection, recording and quality. Electronic data will be backed up every 24 hours to both local and remote media in encrypted format. Study data will be retained for 10 years following the completion of the research.

13 PEER AND REGULATORY REVIEW

The study has been peer reviewed in accordance with the requirements outlined by UCLH. The Sponsor considers the procedure for obtaining funding from NIHR to be of sufficient rigour and independence to be considered an adequate peer review. The study was deemed to require regulatory approval from the following bodies: the NHS Health Research Authority and Research Ethics Committee. Each approval will be obtained before the study commences.

14 ASSESMENT AND MANAGEMENT OF RISK

The risk to participants in this study is deemed low. All investigations involved in data collection are non-invasive and are not expected to cause any discomfort. However, both spirometry and respiratory muscle strength assessment are maximal tasks, requiring maximal effort, and may result in a level of fatigue. The Chief Investigator is fully trained in all these procedures and will be sensitive to any fatigue and pace activities accordingly. Participants will also be free to withdraw should they find any investigation uncomfortable.

The questionnaires included in data collection are widely used in clinical practice and not expected to cause any emotional distress to participants. That said, participants will be told that should they find any questions difficult/upsetting to answer, they can skip those questions.

15 RECORDING AND REPORTING OF EVENTS AND INCIDENTS

15.1 Definitions 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**,

Term	Definition
	• 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.	

15.2 Assessments of Adverse Events

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

15.2.1 Severity

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

15.2.2 Causality

The assessment of relationship of adverse events to the procedure is a clinical decision based on all available information at the time of the completion of the case report form.

The following categories will be used to define the causality of the adverse event:

Category	Definition
Definitely:	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably:	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the study

Category	Definition
	procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant events).
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study procedure). There is another reasonable explanation for the event (e.g. the participant's clinical condition).
Not related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

15.2.3 Expectedness

Category	Definition
Expected	An adverse event which is consistent with known expected reactions to included procedures, namely, transient dizziness or bronchoconstriction immediately following spirometry.
Unexpected	An adverse event which is not consistent with known reactions to included procedures, as mentioned above.

15.3 Recording adverse events

All adverse events immediately following data collection will be recorded in the CRF following consent. All adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event

The participant's involvement in the study will terminate at the end of the single session of data collection, and as no adverse reactions are expected outside of this timeframe, they will not be formally followed up to record adverse events after this.

15.4 Procedures for recording and reporting Serious Adverse Events

All serious adverse events will be recorded in the CRF and the sponsor's AE log.

All SAEs (except those specified in section 16.5 as not requiring reporting to the Sponsor) must be recorded on a serious adverse event (SAE) form. The CI/PI or designated individual will complete an SAE form and the form will be preferably emailed to the Sponsor within 5 working days of becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible.

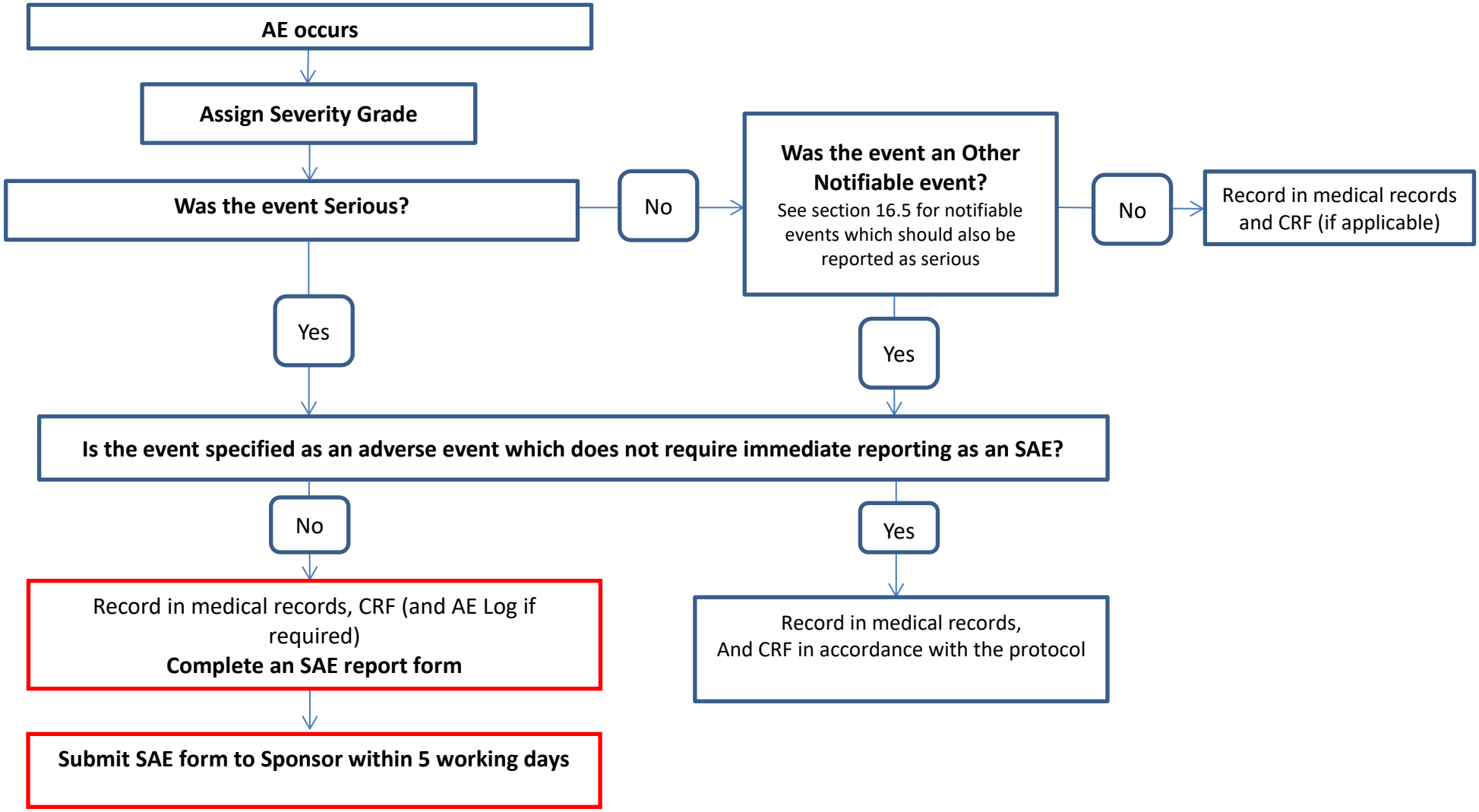
Where the event is unexpected and thought to be related to the procedure this must be reported by the Investigator to the Health Research Authority within 15 days.

Completed forms for unexpected SAES must be sent within 5 working days of becoming aware of the event to the Sponsor

Email forms to randd@uclh.nhs.uk (if sponsored by UCLH)

Research-incidents@ucl.ac.uk (if sponsored by UCL)

Flow Chart for SAE reporting (this simple flow chart is for single site study, please amend in line with study specific requirements)



15.6 Reporting Urgent Safety Measures

If any urgent safety measures are taken the CI/ PI 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.

15.7 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 CI 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 CI and sponsor will be notified immediately of any case where the above definition applies during the study conduct phase.

15.9 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.

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

16 MONITORING AND AUDITING

Participants will have undergone nasendoscopy as part of their usual care in voice clinics at the four research sites. These procedures will take place prior to identification for this study and will be undertaken by expert clinicians who are trained in these procedures. The Chief Investigator will inform the sponsor should he have concerns which have arisen once the images are viewed.

17 TRAINING

The Chief Investigator will be working on this study alone. He will be trained in all methodologies employed in the study as part of his NIHR DCAF award training plan, including

speech-breathing assessment and formal training and certification in spirometry performance and interpretation.

18 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 UCLH. A collaboration agreement is also in place between UCLH and KCL, as academic host to the researcher's PhD, which further specifies that UCLH will grant license to KCL to use IP for certain purposes.

19 INDEMNITY ARRANGEMENTS

UCLH will provide NHS indemnity cover for negligent harm, as appropriate and is not in the position to indemnify for non-negligent harm. NHS indemnity arrangements do not extend to non-negligent harm and NHS bodies cannot purchase commercial insurance for this purpose; it cannot give advance undertaking to pay compensation when there is no negligence attributable to their vicarious liability. The Trust will only extend NHS indemnity cover for negligent harm to its employees, both substantive and honorary, conducting research studies that have been approved by the R&D Department. The Trust cannot accept liability for any activity that has not been properly registered and Trust approved. Potential claims should be reported immediately to the Joint Research Office.

20 ARCHIVING

UCLH recognises 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 study master file will be archived at UCL in accordance with the UCLH Standard Operating Procedure 10 Archiving of Investigator Site File (ISF) and Pharmacy Site File (PSF). It will be archived for a minimum of 5 years from the study end, and no longer than 30 years from study end.

21 PUBLICATION AND DISSEMINATION POLICY

The results of this study will be written up for open-access publication. Results are also planned to be presented at the Voice Foundation's Annual Care of the Professional Voice Symposium as well as various professional events and study days (for example Speech and Language Therapy Clinical Excellence Network (CEN) events).

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23 APPENDICES

23.1 Table of outcomes

Variable	Source	Time point	Collect by	Purpose	Standardised	Data type
Lung Volume Initiation	Procedure	Research session	DCAF	Main outcome	Procedure [31]	Continuous
Lung Volume Termination (LVT)	Procedure	Research session	DCAF	Secondary outcome	Procedure [31]	Continuous
% Vital capacity per syllable (%VC/syl)	Procedure	Research session	DCAF	Secondary outcome	Procedure [31]	Continuous
% Ribcage contribution (%RC)	Procedure	Research session	DCAF	Secondary outcome	Procedure [31]	Continuous
Speech rate	Procedure	Research session	DCAF	Secondary outcome	Procedure [31]	Continuous
Utterance length	Procedure	Research session	DCAF	Secondary outcome	Procedure [31]	Continuous
Effort level	Procedure	Research session	DCAF	Secondary outcome	Ad-hoc visual analogue scale	Continuous
Bowing Index	Electronic data/images	Participant identification/ Routine care	Clinician	Exploratory outcome	Standardised[37]	Continuous
Closure pattern	Electronic data/images	Participant identification/ Routine care	Clinician	Exploratory outcome	Standardised[38]	Categorical
Supraglottic activity	Electronic data/images	Participant identification/ Routine care	Clinician	Exploratory outcome	Standardised[38]	Ordinal
Forced Vital Capacity	Procedure	Research session	DCAF	Secondary outcome	Standard lung function metric	Continuous
Peak expiratory flow	Procedure	Research session	DCAF	Secondary outcome	Standard lung function metric	Continuous
Forced volume in 1 second	Procedure	Research session	DCAF	Secondary outcome	Standard lung function metric	Continuous
Maximum expiratory pressure	Procedure	Research session	DCAF	Secondary outcome	Standard respiratory test[39]	Continuous
Maximum inspiratory pressure	Procedure	Research session	DCAF	Secondary outcome	Standard respiratory test[39]	Continuous
Laryngeal resistance	Procedure	Research session	DCAF	Secondary outcome	Standardised[40]	Continuous
Aging Voice Index	Questionnaire	Research session	DCAF	Secondary outcome	Standardised[41]	Continuous
Cincinnati Dyspnea Questionnaire	Questionnaire	Research session	DCAF	Secondary outcome	Standardised[42]	Continuous
Acoustic Voice Quality Index	Procedure	Research session	DCAF	Secondary outcome	Standardised and validated[43]	Continuous
Consensus Auditory-Perceptual Evaluation of Voice	Procedure	Research session	DCAF	Secondary outcome	Gold standard perceptual voice assessment[44,45]	Continuous

DCAF: Doctoral Clinical Academic and Practitioner Fellow (the researcher)