Protocol for a non-Investigational Medicinal Product (IMP)

This guide is to help researchers with the design and content of protocols for randomised trials that do not involve Investigational Medicinal Product (IMP). It provides advice on the important information that should generally be included in a protocol including some of the methodological considerations specified within Good Clinical Practice (GCP). Further advice can be obtained from the Research Directorate.

General Information

Title**: Is trans-laryngeal ultrasound (TLUS) a useful tool to evaluate the vocal fold movement abnormalities seen in Inducible Laryngeal Obstruction (ILO) a pilot study**

Full names, roles and contact details – for Chief Investigator,
Principle Investigator: Claire Slinger Consultant Speech & Language Therapist, Lancashire Chest Centre
Collaborator: Dr Kina Bennett
Collaborator: Miss Jodi Allen, National Hospital for Neurology and Neurosurgery, London
Collaborator: Dr Roganie Govender, University College, London
Collaborator: Dr Richard Slinger, Consultant Clinical Psychologist, Lancaster University
Collaborator: Sally Richmond, Head and Neck Sonographer, Imperial College Hospital

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List of abbreviations and definitions:

US Ultrasound
TLUS Trans-Laryngeal Ultrasound
ILO Inducible Laryngeal Obstruction
SLT Speech & Language Therapist
LTHTR: Lancashire Teaching Hospitals NHS Trust
RPH: Royal Preston Hospital
PI: Principal Investigator

Background Information:

1. **A rapid review and critical appraisal has been conducted and published here**
   Allen, J.E., Clunie, G.M., Slinger, C., Haines, J., Mossey-Gaston, C., Zaga, C.J., Scott, B., Wallace, S. and Govender, R. (2021), Utility of ultrasound in the assessment of swallowing and laryngeal function: A rapid review and critical appraisal of the literature. International Journal of Language & Communication Disorders, 56: 174-204. https://doi.org/10.1111/1460-6984.12584

2. **Translating Ultrasound into Clinical Practice for the Assessment of Swallowing and Laryngeal Function: A Speech and Language Pathology-Led Consensus Study.**
   Allen JE, Clunie G, Ma JK, Coffey M, Winiker K, Richmond S, Lowell SY, Volkmer A. Dysphagia. 2022 Feb 24:1–13.. Epub ahead of print. PMID: 35201387; PMCID: PMC8867131. doi: 10.1007/s00455-022-10413-9
   https://pubmed.ncbi.nlm.nih.gov/35201387/

A further piece of work via an International Ultrasound group I am active in is currently undertaking writing up of a NGT nominal group theory process around transition of the use of US into clinical practice.

Background:

This two-stage study is a pilot to inform further investigations of the feasibility of using ultrasound to view the vocal cords (trans laryngeal ultrasound or TLUS) as a method of looking at vocal cord movements on breathing in. Stage one will look at a population of healthy volunteers. Stage two will look at a cross-section of patients referred to our airways service for assessment of breathlessness.

When healthy, the vocal cords open during breathing in to maximise ventilation. If the vocal cords narrow when breathing in, this can lead to breathing difficulties, and is known as Inducible Laryngeal Obstruction, or ILO. ILO refers to the inappropriate adduction of the vocal folds and or supraglottic structures (above the vocal cords) on inspiration (Christensen et al). ILO is currently coded as ICD 10 Code J38.7 - other disease of larynx.

ILO presents with asthma-like symptoms and is recognised as a "treatable trait" of asthma (ERS, 2020). ILO can make management of acute and chronic "brittle" asthma more challenging, as it is often treated inappropriately medically with high medication burden and high healthcare utilisation, including unnecessary intubation (Newman et al, 1995; Haines et al, 2020; Murphy et al, 2020).

Patients referred for assessment for refractory breathlessness to our Tertiary referral service routinely undergo a diagnostic video laryngoscopy to assess for ILO. This is the current gold standard for assessment and confirmation of diagnosis of ILO. However, accessibility to laryngoscopy for the diagnosis of ILO is limited outside of a specialist centre, and out of hours, even within specialist severe asthma & airways units. Additionally, laryngoscopy is an invasive procedure, and some people cannot tolerate it. Therefore, there is interest to look at supporting investigation into the potential use of less invasive methods of assessing vocal cord movement on breathing in.

Currently, Ultrasound (US) is not widely used as part of the speech and language therapy (SLT) clinical toolkit. Ultrasound assessment of laryngeal function has been described extensively within the literature (Noel et al. 2020) and reported to be a viable method to assess vocal fold function in a population of patients after thyroidectomy (Da Costa et al. 2019).

The COVID-19 pandemic has restricted access and provision of standard SLT procedures including laryngoscopy, due to the risk of increased aerosol generation and disease transmission (Tran et al. 2012, Bolton et al. 2020, RCSLT 2020). Timely access to invasive diagnostic procedures, such as laryngoscopy has therefore been reduced from both staffing capacity and due to infection control and risk of transmission in COVID-19 positive patients.

Ultrasound is a potential addition to SLT instrumental tools as it is a non-invasive, non-ionising and non-aerosol-generating procedure that could be delivered at the bedside in a timely manner to assess laryngeal function. The use of ultrasound to identify patients who may have vocal cord movement impairments, such as vocal fold palsy and paresis has been shown to have high sensitivity and specificity in a recent systematic review and meta-analysis (Allen, Clunie & Slinger, et al 2020).

The importance of recognising if a patient has ILO:
The true prevalence of ILO is thought to be underestimated, with the European Respiratory Society and European Laryngological Society reporting that between 24% and 53% of patients with severe asthma have ILO. The prevalence of ILO in all asthma is estimated as 10% of the population.

Currently, there are approximately 5.4 million people in the UK receiving treatment for asthma. Therefore, potentially over half a million people in the UK may have ILO, the majority of whom may be undiagnosed.

Severe asthma affects 5 to 10% of the asthma population but consumes a disproportionate amount of the global asthma budget (~50%) due to unscheduled health care utilisation in primary care, hospitalisations due to severe exacerbations, and the costs of pharmacotherapy, some of which may not be necessary.

A recent systematic review (Lee et al 2020) highlighted ILO as a comorbidity in quarter to a half of asthma cases. In two prospective studies of difficult-to-treat asthma where ILO was suspected, up to 50% of patients were identified as suffering both ILO and asthma. (Low et al 2011, Forrest et al 2012).

A study from the Asthma UK Centre in Applied Research has found that asthma costs the UK health service at least £1.1 billion each year. A UK-wide study, by the Asthma UK Centre for Applied Research, found that there were around 6.4 million GP and nurse consultations for asthma each year. Around 100,000 people are admitted to hospital each year because of asthma attacks.

Of the £1.1b cost of treating asthma in the UK, at least £666 million is spent on prescription costs each year. Other costs include £160m on GP consultations, £143m on disability claims and £137m on hospital care.

In a systematic review and meta-analysis (Murphy et al 2021), patients with comorbid Asthma and ILO accessed healthcare services 39% more than those with Asthma only (n=177/3 studies). ILO intervention by SLT reduced the number of times patients accessed health services by 50.5% (n=275/3 studies) and enabled 74% of patients to reduce or stop Asthma medication (n=191/4 studies).

A statement of the current service / practice and the relevance of this study to current or new practice:
Therefore, the potential for early diagnostic screening with TLUS may help identify patients with asthma who also have ILO as treatable trait. If this can be identified, this may help to reduce both healthcare utilisation, allowing health resources to be used more appropriately, and have potential significant impact on morbidity for patients and their families, with potential for significant patient benefit.

Additionally, the prevalence of ILO is thought to be greater in the paediatric population. Therefore, if this study were to prove utility of TLUS in an adult population, there would be potential to evaluate its use in a paediatric population, to prevent any unnecessary treatment escalation and morbidity, as well as offering a less-invasive procedure with potential to be well-tolerated.

Aims & Objectives:

This two-stage pilot study aims to evaluate whether trans laryngeal ultrasound (TLUS) can be a useful tool in the assessment of the abnormal vocal fold movements on inspiration seen in ILO.

The purpose of the two stages of this study is to assess if the use of TLUS is a useful triage screening tool in the assessment of ILO when compared to the current gold-standard reference test of video-laryngoscopy.

Stage one will be conducted with healthy NHS volunteers from the host organisation, (Lancashire Teaching Hospitals NHS Trust) and will look at the degree of success at visualising both vocal cords (right and left), at baseline, during breathing, and when mimicking ILO. The experience of undergoing ultrasound assessment will be looked at via a post-ultrasound scan questionnaire.

Stage two will be conducted with a group of up to 30 patients referred to the Tertiary airways service for breathlessness. We will assess vocal cord movements with simultaneous laryngoscopy (usual care) and TLUS, to investigate whether TLUS has utility as a screening tool to assess the vocal fold movement abnormalities seen in ILO.

Primary aims:

To perform analysis of the range of vocal fold movements on inspiration, using TLUS in healthy volunteers and patients referred to a tertiary airways service.

To assess the sensitivity, specificity and positive predictive value of the use of ultrasound in the assessment of ILO, using Laryngoscopy as reference standard.

To investigate the patient and healthy volunteer perspectives of TLUS assessment of the vocal cords.

Secondary aims

To provide recommendations to inform the development of SLT-led US protocols and make suggestions for further research for its use in assessment of ILO.

To gather information to inform such a protocol, such as impact of age, gender, frequency of probe and approach used to assess vocal fold movement (lateral longitudinal, anterior, thyrohyoid, or crico-thyroid membrane).

To inform the use of static and dynamic assessment techniques using TLUS.

To begin to collect data on variation of vocal fold adduction on inspiration in healthy adults.

To understand how to begin to collect information on measurements of the glottis on inspiration in healthy adults and patients who have confirmed ILO on laryngoscopy.

To collect data on measurements of vocal fold closure associated with a positive diagnosis of ILO.

Interventions
There are no known risks to the patient in the use of laryngeal Ultrasound. The treatment is non-invasive and does not involve radioactive substances.
As the patient will be undergoing usual care, there is no risk of missing an ILO diagnosis.

The treatments will be performed by the PI (CS) and laryngoscopy by the SLT involved in the patient's usual care. After assessment and diagnosis, patients will continue along their usual care pathway, i.e., if ILO is confirmed they will be offered SLT intervention for ILO, and if ILO is not confirmed will continue along the Asthma pathway for medical management.

Proposed methods:

Stage one: healthy controls:
Volunteers will be recruited from NHS staff at the host organisation (LTHTR). Healthy volunteers will be given an information leaflet and consent form upon providing an expression of interest.

Informed consent will be taken by the PI from healthy volunteers who decide to go ahead. It will be stressed that participation and consent can be withdrawn at any time. The consent process itself will take place before the procedure and will be taken by the PI (CS). Consent will be taken in a separate and private room (either the booking-in room in the endoscopy department at RPH, or a separate clinic room in the chest Clinic). This will be completed before the procedure and before entry into the room where the ultrasound procedure will take place.

The consent forms will be stored in a locked cabinet in PI's office. Longer-term, study documents including data and investigator site files will be archived at the Trust's off site archiving facility following local procedures.

Healthy volunteers will be allocated a time and date to attend Chest clinic, or the Endoscopy department at the host organisation, Royal Preston Hospital (RPH) for the scanning session. The scan will be carried out in a private room using transmission gel. Access only to the neck area is required, with privacy and dignity always respected.

The PI will perform an US scan of the larynx, using the Vscan Air (GE), using a protocol designed by the PI. The scan is recorded and stored securely using GE's system. A proportion of scan will be sent to the study collaborator (Jodi Allen) and a Specialist Head & Neck Sonographer securely and anonymously with no patient identifiable information included in order to confirm findings when there is uncertainty, and in order to ensure inter-rater reliability.

The scan will consist of a "sweep" of the larynx to identify the main landmarks (hyoid bone, thyroid cartilage, arytenoid cartilages, vocal cords and false vocal cords). A recording form has been prepared for ease of recording. An anonymised code number will be assigned to the Healthy volunteer.

A record will be taken of the frequency in MHz and depth that successful visualisation of the vocal cords occurred to help inform future studies and refine the protocol. Any other factors that are deemed useful to include to help replicate findings and improve image quality and scanning success will also be recorded (such as gain used, high or low, and approach transverse, or lateral longitudinal, and the use of any pre-sets such as Neo-head, lung or small parts).

When the vocal cords are visualised, the healthy volunteer will be asked to breathe normally, take 3 deep inspirations, and then, say "ee" for a sustained period. They will then be asked to breath hold, then take a deep breath in (3 trials), and then mimic ILO (the PI will discuss how to do this before the scan takes place). The commands for each of the above will be in the same order for each patient, as there is no accompanying sound, this will allow for easier analysis to be able to differentiate each vocal cord movement according to what the volunteer was asked to do.

Following the procedure, the volunteer will be given an electronic questionnaire to complete, so that feedback on their experience can be gained and used as part of writing up of findings.
https://forms.office.com/pages/designpagev2.aspx?lang=en-US&origin=OfficeDotCom&route=Start&subpage=design&id=gmOokJ_8nEW5GphS-wiyzcq-VqpQSdVGguxTgVT2MfRUMEZUNUoxT1YyQklPOEVVM0VQVVpJRUVEUS4u

Stage two: patient population

A sample of 30 participants will be recruited from consecutive patients referred to our NHS Tertiary Airways service for assessment for complex breathlessness and ILO. Participants will be asked at initial assessment, after they have consented to the laryngoscopy, if they would wish to undergo TLUS concurrently with their usual care of diagnostic laryngoscopy.

An information leaflet will be given, and written consent form completed with the patient by the PI. Written Information will be provided at the point of initial consultation (at least 48 hours before the planned procedure. Written consent will take place at the appointment for the Laryngoscopy (usual care for laryngoscopy), by the PI (CS). A witness will not be present. Consent will take place in a private booking-in room that is part of usual care for patients attending for laryngoscopy assessment for ILO). Patients have more than 48 hours to consider the information and decide if they would like to participate.
Patients who require an interpreter for their initial consultation will be provided with information via the interpreter of the study.

Patients will be informed that usual care will not be affected by their decision to participate or not, and that consent can be withdrawn at any point. If the patient finds dual assessment with laryngoscopy and TLUS too invasive or distressing, they can withdraw consent, and the TLUS will be stopped.

It is envisaged that the TLUS operator (PI) will perform the US assessment whilst another SLT completes the laryngoscopy (usual care) and works through the usual diagnostic laryngoscopy provocation protocol to induce symptoms. The US-operating SLT will take a note of settings to achieve image acquisition and will take note of vocal fold movements on an anonymised recording form with subject allocation number identified.

The SLT operators (TLUS and laryngoscopy) will be blinded to the images and results of the other assessment (either TLUS or laryngoscopy), as the screen for the Laryngoscopy system can be rotated away to be unobservable by the US-operator SLT. Following the procedure, the SLT conducting the US will leave the endoscopy theatre room to allow for usual debrief to occur with the patient (usual care). After this, the patient will be asked to complete a short questionnaire electronically to elicit their experience of TLUS.
https://forms.office.com/pages/designpagev2.aspx?lang=en-

US&origin=OfficeDotCom&route=Start&subpage=design&id=Ec2bnHqXnE6poLxzQJAWSvzsRL8eSdVDg6YlWzFhtWZUMlkwUkdJQjNTTUNVRkVJTU9RUDBCNjAwOS4u

Following the clinical session, the results of the TLUS and laryngoscopy will be compared for outcome and record made (on the reporting form) of the assessments compared, and any false positive or negative results will be documented, along with ability to visualise either or both vocal folds (left and right).

Data collection and handling:
Written recording forms will be marked with an anonymous participant code. Data from recording forms for stage one and stage two will be extracted and inputted into the SPSS statistical analysis package by the PI. Recording forms will be stored in a locked filing cabinet in the SLT NHS office.
Data from participant questionnaires from stage one and stage two will be downloaded from Microsoft Forms into a Microsoft Excel database. All digital database files will be stored on a password-protected NHS laptop. Long-term arrangements: Study documents including data and investigator site files will be archived at the Trust's off site archiving facility following local procedures.

The Vscan Air ultrasound system allows clinicians to securely share data and images and includes sharing auto-anonymized images with other apps, with no cloud requirement.

Images will be stored on a NHS laptop which is password protected and will be stored in a password-protected file.

All data will be anonymised via a combination of identifier as a healthy volunteer (HV) or patient (PT) and participant number, followed by the date of clinic (e.g HV1 18.07.22, or for patients PT118.07.22).

Data for healthy volunteer and patients will be analysed by the Principal Investigator electronically on an NHS laptop.

Advice will be sought from LTHTR research team regarding support for statistical analysis of data, but all patient identifiable data will be removed before this stage.

Research data will be stored electronically, which will comprise scanned consent forms and questionnaires, US and laryngoscopy images, examination data recording sheets and statistical data. Electronic data will be stored on the NHS Trust server in a password-protected folder, accessed only by the Principal Investigator.
Study documents including data and investigator site files will be archived at the Trust's off site archiving facility following local procedures.

Identifiable personal data for the healthy volunteers or the patient participants will not be used for either stage 1 or 2.

Healthy volunteer consent forms and any data will be kept in a separate file, and no access to medical records will be made for these patients. The local SOP for Research with Health Volunteers will be followed.

Data analysis:
The outcomes of the TLUS and laryngoscopy assessments in stage one and stage two and will be analysed using SPSS. 2 x 2 tables will be generated to calculate values of sensitivity (whether a participant can be confirmed as having ILO, or mimicked ILO) and specificity (whether ILO, or mimicked ILO, can be ruled out for a participant), and confidence intervals for visualisation of the vocal folds using TLUS. In stage two, percentage agreement between TLUS and laryngoscopy for confirmation or non-confirmation of ILO will also be calculated.

The values, if available, for measurements of the distance between the arytenoids for healthy volunteers and patients during normal breathing, deep inspiration, and during ILO (mimic in stage 1 and actual in stage 2), will be analysed via a non-parametric comparison of means within SPSS.

Quantitative questionnaire data will be analysed using Microsoft Excel to generate mean values and ranges. Qualitative questionnaire data will be analysed using thematic analysis (Braun and Clarke, 2006), with themes generated to aid understanding of participants' experiences of the TLUS and laryngoscopy procedures.

Study end definition:

- The study will end when the last participant has been completed and data has been collected. The study will close early if it is found during stage 1 that ultrasound is not useful (limited successful viewings of the vocal folds) in the assessment of vocal fold function.
- The trial will be discontinued if the feedback from patients is adverse for the experience of LUS, or in the case of any adverse events.

Monitoring, Reporting and Finance

- The study will be conducted in accordance with approvals and advice from relevant groups e.g., Ethics and R&D Trust approval.
- The study will be conducted in compliance with the Research Governance Framework for Health and Social Care, the Medicine for Human Use (clinical trials) Regulation 2004 and Good Clinical Practice.
- No Financial agreements have been arranged.

Reporting and Dissemination
Feedback will be given to patients via a poster in the waiting room, along with a scientific poster if successful accepted abstract.

Adapted from Southampton University Hospital Trust and United Bristol Healthcare NHS Trust Research and Development information sheets - Guide to writing a protocol for a non-Investigational Medicinal Product (IMP) randomised trial.