Liverpool University Hospitals
NHS Foundation Trust

Study Protocol

Study Title: Safe and Effective Headgear Accessory for Exercise-Induced Laryngeal Obstruction Studies (HALOS) – a Device Development Study

Internal Reference No: SP0707

IRAS Project ID: 293234

EUDAMED: n/a

UDI: n/a

Version No: 1.0

Date: 22nd Sept 2021

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the **Liverpool University Hospitals NHS Foundation Trust** SOPs, and other regulatory requirement.

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

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of Liverpool University Hospitals NHS Foundation Trust

Signature: ..... Date: ...../...../.....

Name (please print): H. Rogers .....

Position: Research Governance Manager .....

Chief Investigator:

Signature: ..... Date: 22/Sep/2021

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Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host (s), regulatory authorities, and members of the Research Ethics Committee.

TABLE OF CONTENTS

1. AMENDMENT HISTORY

Initial version 1.0 issued 22/Sep/2021

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

2. SYNOPSIS

Study Title	Safe and Effective Headgear Accessory for Exercise-Induced Laryngeal Obstruction Studies (HALOS) – a Device Development Study.
Internal ref. no.	SP0707
Type of study	Interventional
Trial Design	Single Group Assignment.
Trial Participants	Adults with suspected Exercise-Induced Laryngeal Obstruction (EILO) capable of undertaking a Continuous Laryngoscopy during Exercise (CLE) test.
Planned Sample Size	30 participants.
Follow-up duration	There will be no follow-up.
Planned Trial Period	12 months.
Primary Objective	Ensure the HALOS headgear is suitable for facilitating CLE tests.
Secondary Objectives	• Validate risk scores identified in risk management documentation. • Validate mitigations of hazards identified in risk management documentation. • Uncover previously unforeseen hazards, especially any related to usability.
Primary Endpoint	**Device effectiveness**, measured by the proportion of CLE tests where the endoscopy image was clear and stable enough to allow a diagnosis of EILO to be confirmed or ruled out.
Secondary Endpoints	**i) Device usability rating**, measured by the fraction of subjective usability ratings ≥ 4 on the post-test questionnaire. Clinician-reported usability will be scored on a five-point LIKERT scale[1] ranging from 1 (very hard to use) to 5 (very easy to use). Observations will be made throughout the session. **ii) Device usability subjective feedback**, focussing on any clinician-reported concerns regarding set-up, operation and cleaning. **iii) Device tolerability ratings**, measured by the fraction of subjective tolerability ratings ≥ 3 on the post-test questionnaire. Participant-reported tolerability will be scored on a four-point LIKERT scale ranging from 1 (very intolerable) to 4 (very tolerable). **iv) Device tolerability subjective feedback**, focussing on any participant-reported concerns regarding the comfort of the headgear including how hot their head felt, weight of the headgear, how secure the headgear felt and the impact of the headgear on their performance during the investigation.
Device Name	Headgear Accessory for Laryngeal Obstruction Studies (HALOS)

[1] The LIKERT scale is a widely used type of psychometric response scale in which responders specify their level of agreement to a statement typically in five points (Preedy & Watson, 2010). Empirical evidence shows this scale has 90% reliability and 89% validity (Louangrath, 2018).

Manufacturer Name	Medical Physics and Clinical Engineering, Liverpool University Hospitals NHS Foundation Trust
Principle intended use	The device is intended to be used with an endoscope and enable the larynx to be observed during CLE tests. It is intended for use on patients with suspected EILO.
Length of time use the device has been in use.	The device is not currently in use as this is a new design.

3. ABBREVIATIONS

AE	Adverse event
ADE	Adverse Device Effect
CI	Chief Investigator
CLE	Continuous Laryngoscopy during Exercise
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Clinical Trials
CTA	Clinical Trials Authorisation
EILO	Exercise Induced Laryngeal Obstruction
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
LUHFT	Liverpool University Hospitals NHS Foundation Trust
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NRES	National Research Ethics Service (previously known as COREC)
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&I	R&I Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SIL	Subject Information Leaflet (see PIL)

SOP	Standard Operating Procedure
TMF	Trial Master File
USADE	Unanticipated Serious Adverse Device Effect

4. BACKGROUND AND RATIONALE

4.1 Condition

Exercise-induced laryngeal obstruction (EILO) is a condition in which closure of the larynx occurs during high-intensity exercise. The reduction in airflow due to airway narrowing results in breathlessness and wheeze, and the patient may also report a cough or throat discomfort that can persist for some time (Hall, et al., 2016).

Whilst symptoms usually resolve soon after stopping exercise, an episode of EILO can impact on athletic performance and in competitive sports people can thereby impact on their careers. In all individuals, sudden onset EILO can lead to breathlessness inducing significant fear, panic, loss of control and pain (Carel, et al., 2015).

4.2 Current Practice

Due to the presentation of the condition, there is a large differential diagnosis, and the patient is often diagnosed with exercise-induced asthma (bronchoconstriction) and prescribed a short-acting bronchodilator. However, there are differences between the two conditions. The symptoms in EILO arise during high-intensity exercise and settle rapidly (within 5 minutes of exercise cessation), whereas with exercise-induced bronchoconstriction the symptoms onset following exercise cessation (5-10 minutes). Additionally, the wheeze of EILO is typically high pitched and occurs during the inspiratory phase of the breathing cycle. However, narrowing of the lower airway results in a polyphonic basal wheeze, and occurs during the expiratory phase (Hall, et al., 2016).

Incorrect diagnosis can lead to a large pharmacological burden for the patients with many being incorrectly treated with regular doses of steroids with little or no clinical effect (Newman, et al., 1995; Traister, et al., 2013).

EILO is often diagnosed in young athletes, and a cross-sectional study of 12-13 year-olds in Sweden found a prevalence of approximately 6% (Johansson, et al., 2015). However, a study found that EILO may be as prevalent as exercise-induced bronchoconstriction, and these two conditions may coexist in over 10% of individuals (Nielsen, et al., 2013).

Whilst clinical features can differentiate EILO from exercise-induced bronchoconstriction, studies have shown that discriminatory questions (e.g. difficulty breathing in when exercise) have a poor diagnostic value. A study has also shown that a diagnosis of EILO cannot be made by resting or post-exercise spirometry, or by peak flow measurement (Christensen, et al., 2013). Additionally, as EILO presents during high-intensity exercise, investigations during resting state may not provide a reliable diagnosis.

Clinicians have observed patients, either in person or by video recording, as they develop symptoms to review the presentation and onset. However, this method of investigation has not yet been formally studied (Hall, et al., 2016).

The gold standard for a diagnosis of EILO is a continuous laryngoscopy exercise (CLE) test, in which a flexible endoscope is used to monitor the laryngeal movement in real-time during exercise (Hall, et al., 2016). The tip of the endoscope is positioned in the mesopharynx (identified in Figure 1) by the clinician, who uses the live image from the endoscope to guide its position. A securing headgear is essential to keep the endoscope in a fixed position while the patient exercises, both to achieve a stable image and for the safety of the patient. An example of a CLE test set-up is displayed in Figure 2. This method of investigation is not currently offered by LUHFT, and other centres we have contacted provide the service using a non-CE/UKCA marked headgear.

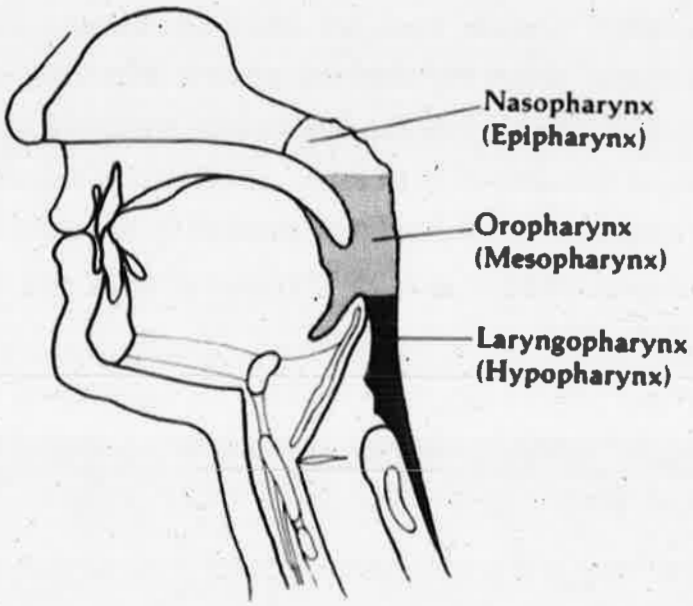

Figure 1: showing the location of the mesopharynx, taken from (James F. Bosma M.D., 1986)

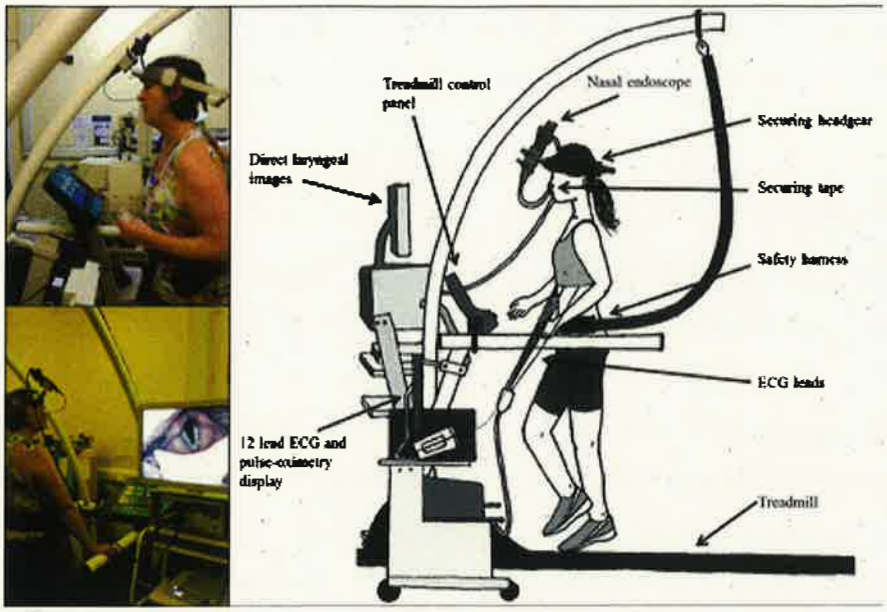

Figure 2: Continuous laryngoscopy exercise (CLE) test (Hall, et al., 2016)

4.3 Existing Research

Studies have been carried out to investigate EILO, and several mention the use of a specialised headgear (Hull, et al., 2019; Heimdal, et al., 2006; Olin, et al., 2016). However, there has been no formal research published regarding the headgear itself.

4.4 Rationale for Current Study

A headgear is necessary to carry out CLE tests for the investigations of EILO, as the endoscope must be kept stable for both image quality and patient safety. There is no commercial option existing on the market at present, and other centres have manufactured their headgear in-house (Liverpool Heart and Chest Hospital (LHCH), Royal Brompton Hospital).

Without a specialised headgear it is not possible to carry out CLE tests at LUHFT, and patients are sent for investigations at LHCH. This study is an essential step in improving the care that can be offered by LUHFT for sufferers of EILO. Evaluating the in-house design of headgear is necessary to support its safe and effective clinical use in accordance with the Medical Device Directive (MDD) 93/42 and in the spirit of the European Medical Device Regulations (MDR) 2017/745. By producing an in-house manufactured headgear, it will enable LUHFT to provide an additional service for patients, avoiding the inconvenience to them of having to travel further afield.

Therefore, the hypothesis for this study is that the HALOS headgear is sufficiently effective for clinical use, and that the risks are understood adequately for an accurate benefit/risk ratio evaluation.

4.5 Regulatory Compliance

The device is intended to be used with an endoscope and enable the larynx to be observed during CLE tests. According to the MDD it is classified as an accessory for a medical device and therefore the MDD would apply. However, the headgear is not intended to be made commercially available or UKCA/CE marked, nor will it be used outside the Trust where it is manufactured. Consequently, as it is not being 'put into service' nor 'placed on the market', it is not subject to the requirements of the MDD. Nonetheless, the headgear has been specified, designed and manufactured following a Quality Management System (QMS) aligned with BS EN ISO 13485:2016 QMS requirements for medical devices, the MDD and European MDR. This includes Post Market Surveillance activities.

5. OBJECTIVES

5.1 Primary Objective

Ensure the HALOS headgear is suitable for facilitating CLE tests.

5.2 Secondary Objectives

Validate risk scores identified in risk management documentation.

Validate mitigations of hazards identified in risk management documentation.

Uncover previously unforeseen hazards, especially any related to usability.

6. TRIAL DESIGN

6.1 Summary of Trial Design

The study is an interventional clinical trial involving a single group of 30 participants undergoing a CLE test with the HALOS headgear.

Participants will be required to attend a single consultation and screening appointment to discuss the investigation procedure, and this will occur at least a week before the CLE test. Participants will then attend one appointment for the CLE test. There will be no follow up assessments using the headgear.

6.2 Primary and Secondary Endpoints/Outcome Measures

6.2.1 Primary Outcome Measure

Device effectiveness, measured by the proportion of CLE tests where the endoscopy image was clear and stable enough to allow a diagnosis of EILO to be confirmed or ruled out.

6.2.2 Secondary Outcome Measures

i) Device usability rating, measured by the fraction of subjective usability ratings ≥ 4 on the post-test questionnaire. Clinician-reported usability will be scored on a five-point LIKERT scale[2] ranging from 1 (very hard to use) to 5 (very easy to use). Observations will be made throughout the session.

ii) Device usability subjective feedback, focussing on any clinician-reported concerns regarding set-up, operation and cleaning.

iii) Device tolerability ratings, measured by the fraction of subjective tolerability ratings ≥ 3 on the post-test questionnaire. Participant-reported tolerability will be scored on a four-point LIKERT scale ranging from 1 (very intolerable) to 4 (very tolerable).

iv) Device tolerability subjective feedback, focussing on any participant-reported concerns regarding the comfort of the headgear including how hot their head felt, weight of the headgear, how secure the headgear felt and the impact of the headgear on their performance during the investigation.

6.3 Trial Participants

6.3.1 Overall Description of Trial Participants

Participants will be patients of the Liverpool University Hospitals NHS Foundation Trust with suspected EILO and who have been selected for CLE testing to confirm the diagnosis.

6.3.2 Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Male, female or non-binary, aged 18 years or above.
- Able (in the Investigators opinion) and willing to comply with all study requirements.

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[2] The LIKERT scale is a widely used type of psychometric response scale in which responders specify their level of agreement to a statement typically in five points (Preedy & Watson, 2010). Empirical evidence shows this scale has 90% reliability and 89% validity (Louangrath, 2018).

- Able to undergo a CLE test as judged by the clinician, and where a clinical need of the test for the delivery of healthcare has been identified.

6.3.3 Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Pain, sore areas, broken skin at the site of contact with the headgear.
- Devices, e.g. cochlear implants, that impede the use of the headgear.
- Head circumference is less than 50cm or greater than 63cm, reflecting the 3rd centile for females and 97th centile for males, respectively (Bushby, 1992).
- Exclusion criteria for endoscopy procedures:
    - Skull base/facial surgery or fracture within the previous six weeks
    - Major or life threatening epistaxis within the previous six weeks
    - Trauma to nasal cavity secondary to surgery or injury within the previous six weeks
    - Sino-nasal and anterior skull base tumours/surgery
    - Nasopharyngeal stenosis
    - Craniofacial anomalies
    - Hereditary haemorrhagic telangiectasia
    - Severe movement disorders and/or severe agitation
    - Vasovagal history
    - Bleeding risks
- Any other exclusion criteria as identified by the current endoscopy procedure.

6.4 Study Procedures

6.4.1 Informed Consent

The participant must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed.

Written and verbal versions of the participant information and Informed consent will be presented to the participants detailing no less than: the exact nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. Participants will be assured that their individual results will be used to help diagnose and treat their breathlessness.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participants. The original signed form will be retained at the study site.

6.4.2 Screening and Eligibility Assessment

The Principal Investigator will review patient records from an existing list of patients awaiting CLE tests. All patients will have been referred for opinion regarding their breathlessness. Participants will be checked for eligibility to enter the study prior to arranging a clinic session. This service is not currently offered by LUHFT.

For all potential study participants, a consultation appointment will be arranged to be conducted at least a week before the investigation appointment. During the consultation, the study will be explained, and the participant will be given the Participant Information Sheet. The screening procedure will be conducted during the consultation appointment. This will involve an eligibility check to ensure that the participant meets the inclusion criteria and none of the exclusion criteria apply, as defined in Sections 6.3.2 and 6.3.3, respectively.

6.4.3 Baseline Assessments

Head circumference, recorded during the investigation appointment.

6.4.4 Subsequent assessments

Following the consultation appointment, the participant will attend one investigation appointment to undergo the CLE test on-site at the Outpatient Department, Alexandra Wing, Broadgreen Hospital. There will be no follow-up assessments.

On the day of the investigation appointment, the Principal Investigator will address any questions or concerns before the investigation begins. If the participant still wishes to partake in the study, signed consent will be obtained from the participant. The right of the participant to refuse to participate without giving reasons will be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons

for doing so should be recorded. In these cases, the participants remain within the study for the purposes of data analysis.

Eligibility will be reviewed for any changes, ensuring that the participant meets the inclusion criteria and none of the exclusion criteria apply. As part of this, the circumference of the participant's head around the forehead will be measured and recorded. Signed consent will then be obtained. The participant will then undergo the CLE test following standard clinical practice.

The order of events of the aspects of the investigation related to the headgear will be:

1. The headgear is prepared for use.
2. The headgear is fitted onto the participant's head.
3. The endoscope is inserted into the participant.
4. The endoscope is fitted onto the headgear.
5. The CLE test is carried out.
6. The endoscope is removed from the headgear.
7. The endoscope is removed from the participant.
8. The headgear is removed from the participant.
9. The headgear is cleaned and stored.

Following completion of the CLE test, the participant will complete a questionnaire:

- How tolerable was the headgear during the investigation?
    1) Highly intolerable
    2) Intolerable
    3) Tolerable
    4) Highly tolerable
- Please tell us any concerns about the headgear, thinking about how comfortable it was, how hot your head felt, the weight of the headgear, how secure it felt and the impact of the headgear on your performance during the investigation.

Following the appointment, the clinician will complete a questionnaire including:

- Was the endoscopy image clear and stable enough to allow a diagnosis of EILO to be confirmed or ruled out? (Note that participants are withdrawn from the study if the

CLE test is unable to allow a diagnosis of EILO to be confirmed or ruled out due to reasons unrelated to the headgear.)

- How easy was it to use the headgear?
    1) Very hard to use;
    2) Hard to use;
    3) Neither hard nor easy to use;
    4) Easy to use;
    5) Very easy to use.
- Please record any concerns about the headgear, thinking particularly about set-up, operation and cleaning.

Data will be handled as detailed in Section 13 Data Handling and Record Keeping.

6.5 Discontinuation/ Withdrawal of Participants from Study Treatment

Each participant has the right to withdraw study at any time. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including:

- Pregnancy
- Ineligibility (either arising during the study or retrospective having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with study requirements
- An adverse event, adverse device effect, serious adverse device effect or unanticipated adverse device effect which results in cessation of the CLE test or inability to continue to comply with study procedures
- Consent withdrawn
- If the participant cannot wear the headgear, e.g. it does not fit.
- If the CLE test is unable to allow a diagnosis of EILO to be confirmed or ruled out due to reasons unrelated to the headgear, e.g. the participant cannot tolerate the endoscopy.

Withdrawn participants will be replaced.

The reason for withdrawal will be recorded in the Case Report Form (CRF).

If the participant is withdrawn due to an adverse event, the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

6.6 Source Data

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, Device, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g., there is no other written or electronic record of data). In this study the CRF will be used as the source document for the participant head circumference, the participant questionnaire results, and the clinician questionnaire results.

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

7. TREATMENT OF TRIAL PARTICIPANTS

7.1 Description of Study Intervention(s)

Two headgears of the same design will be manufactured. The headgear is constructed from a modified safety helmet with a clamp fixed on the front to hold the endoscope, and a counterweight fixed on the back for comfort and stability.

A label will be attached indicating that the device is for use in the HALOS pilot study only by trained individuals. User instructions and training will be provided.

Headgear properties:

- Components:
    - White Hard Hat with Chin Strap (ABS, High-Strength Polyester, Nylon, Polycarbonate, Polyethylene)
    - Clamp (Aluminum)
    - Clamp mount (Steel)
    - Secondary fixture (Steel)

- Endoscope strap (Velcro)
- Chin strap (Velcro)
- Counterweight (steel).

- Weight: 1.5 kg

Below are photos of the HALOS headgear device placed on a dummy head with and without the endoscope inserted.

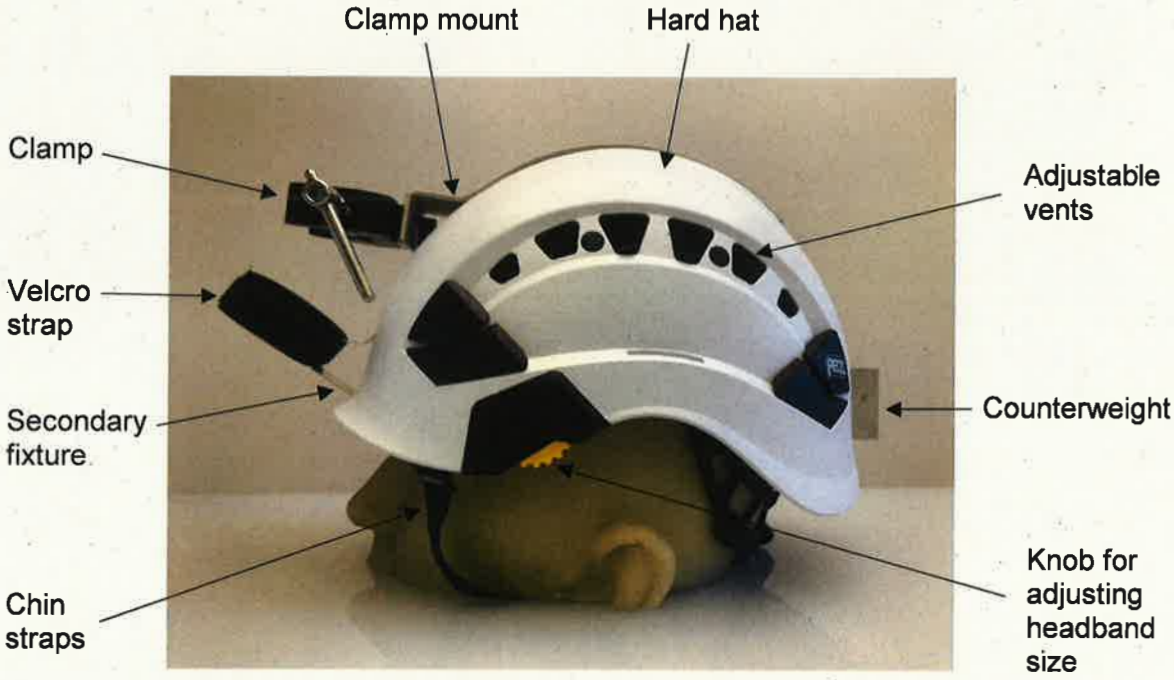

Figure 3: A labelled diagram of the HALOS headgear positioned on a dummy head

Figure 5: A front view of the HALOS headgear positioned on a dummy head

Figure 5: A top view of the HALOS headgear

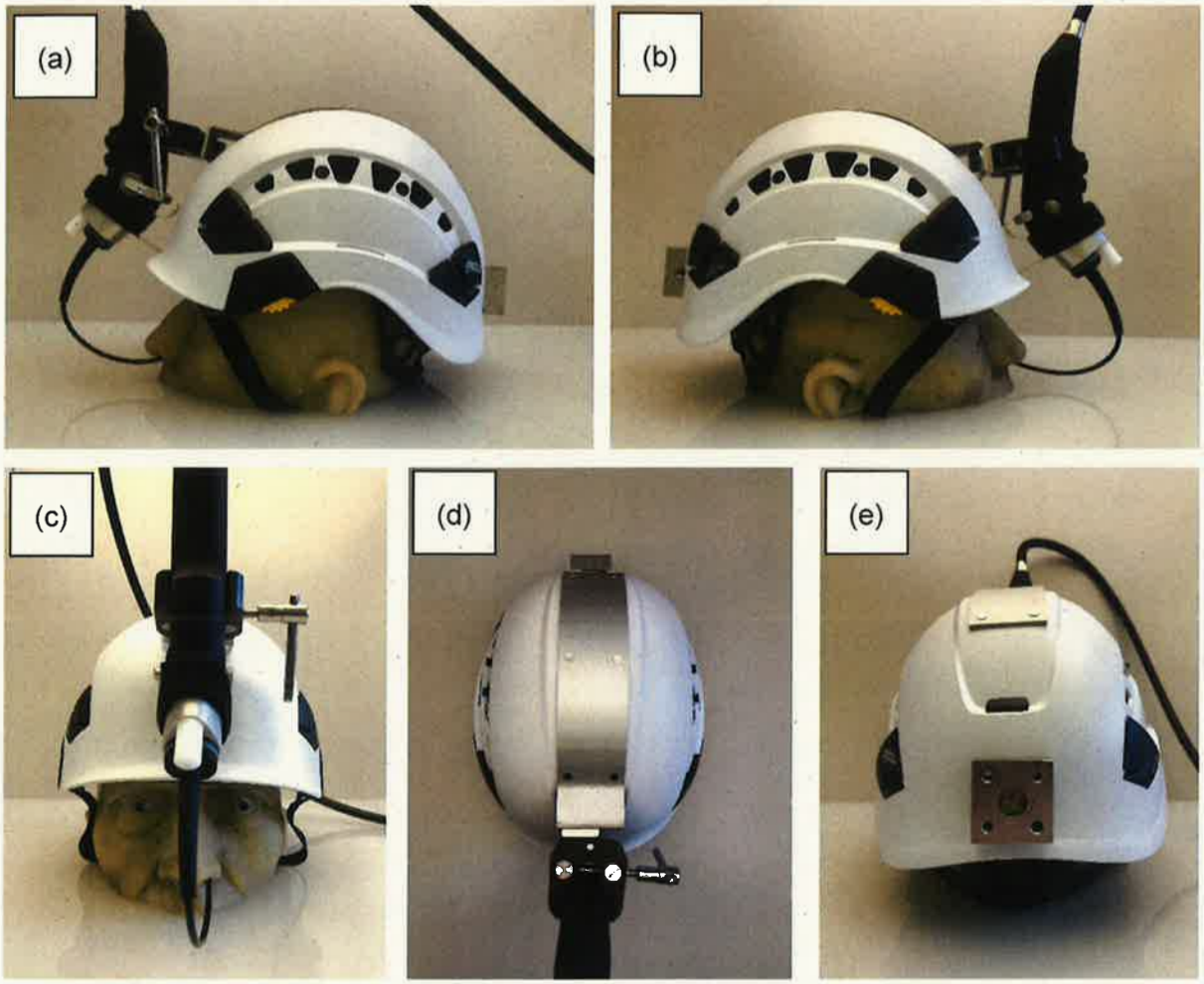

Figure 6: The HALOS headgear with the endoscope inserted positioned on a dummy head, showing views from (a) left side, (b) right side, (c) front, (d) top, (e) back

7.2 Maintenance and storage of device

The two headgear devices will be stored on-site at Broadgreen Hospital, LUHFT, in warm and dry conditions.

After each participant use, the headgear will be thoroughly wiped with disinfectant wipes, and removable fabric straps will be washed with soap and water. Cleaning events will be recorded.

The Velcro strap used to secure the endoscope on the front of the headgear is single-use, and to be disposed of after each participant assessment.

7.3 Risk Management

Device risks are managed by following the Department of Medical Physics and Clinical Engineering Quality Management System, which complies with ISO 14971:2012 Medical

devices – Application of risk management to medical devices. A Risk Management Plan and Risk Assessment are in use.

8. SAFETY REPORTING

8.1 Definitions[3]

8.1.1 Device Deficiency (DD)

This is the inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. Device deficiencies include malfunction, use error and inadequate labelling.

8.1.2 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.

This includes events related to the investigational device or the comparator and events related to the procedures involved (any procedure in the study protocol). For users or other persons, i.e. where the medical occurrence, unintended disease or injury is not in the subject, this definition is restricted to events related to the use of investigational medical devices or comparators.

No potential AEs are identified.

The categories of adverse events are shown in Table 1.

[3] Source: BS EN ISO 14155:2020 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice.

Table 1: Categories of adverse events (taken from BS EN ISO 14155:2020 Table F.1)

<table>
<tr><th>Adverse events</th><th>Non-device-related</th><th colspan="2">Device- or investigational procedure-related</th></tr>
<tr><td>Non-serious</td><td>Adverse event (AE)[a] (3.2)</td><td colspan="2">Adverse device effect (ADE)[c] (3.1)</td></tr>
<tr><td rowspan="3">Serious</td><td rowspan="3">Serious adverse event (SAE)[b] (3.45)</td><td colspan="2">Serious adverse device effect (SADE) (3.44)</td></tr>
<tr><td>Anticipated</td><td>Unanticipated</td></tr>
<tr><td>Anticipated serious adverse device effect (ASADE)[c] (3.1, Note 1 to entry)</td><td>Unanticipated serious adverse device effect (USADE) (3.51)</td></tr>
<tr><td colspan="4">[a] Includes all categories.
[b] Includes all categories that are serious.
[c] Includes all categories that are related to the device or the investigational procedure.</td></tr>
</table>

8.1.3 Serious Adverse Event (SAE):

SAE is an adverse event that led to any of the following:

- death
- foetal distress, foetal death or congenital abnormality or birth defect including physical or mental impairment.
- serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:
    - a life-threatening illness or injury
    - a permanent impairment of a body structure or a body function including chronic diseases
    - in-patient or prolonged hospitalisation
    - medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function

Planned hospitalisation for a pre-existing condition, or a procedure required by the Study Protocol, without serious deterioration in health, is not considered a serious adverse event.

8.1.4 Adverse Device Effect (ADE)

Adverse event related to the use of an investigation medical device. This includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This includes the comparator if the comparator is a medical device.

All AEs judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the device qualify as ADEs. For guidance on causality assessment, refer to MEDDEV 2.7/3 Clinical Investigations: Serious Adverse Event Reporting Under Directive 90/385/EEC and 93/42/EEC.

8.1.5 Serious Adverse Device Effects (SADE):

Adverse device effect that has resulted in any of the consequences of a serious adverse event.

All cases judged by either the reporting medically qualified professional or the sponsor.

8.1.6 Unanticipated Serious Adverse Device Effect (USADE):

Any serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment.

8.2 Reporting of AEs

All AEs occurring during the study observed by the investigator or reported by the participant, whether or not attributed to the device under investigation, will be reported, without undue delay, to the Chief Investigator and LUHFT R&D and recorded on the hospital incident reporting system, in the source data (medical notes) and the CRF. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

8.3 Reporting of DDs/SAEs/SADEs/USADEs

All SAEs, SADEs, and USADEs will be reported to the sponsor/legal representative, Chief Investigator and LUHFT R&D **immediately**; regardless of relationship to the device. DDs that might have led to an SADE if suitable action had not been taken, intervention had not been made or if circumstances had been less fortunate are similarly reported. All SAEs, SADEs and USADEs will be recorded on the hospital incident reporting system, in the source data (medical notes) and the CRF.

Reports of related and unexpected SAEs should be submitted to the Research Ethics Committee (REC) within 15 days of the Chief Investigator becoming aware of the event, using the SAE report form for non-CTIMPs published on the HRA website[4].

All reporting to LUHFT R&D should be by email to RGT@rlbuht.nhs.uk giving as much information about the incident as possible, and should be signed by the PI or Co-investigator. The LUHFT SADE reporting form should be used for LUHFT sponsored studies.

The LUHFT R&D Department will undertake an initial review of the information and ensure it is reviewed. Events will be followed up until resolution, any appropriate further information will be sent by the research team in a timely manner.

8.4 Safety Reports

In addition to the above reporting the Chief Investigator will submit on request a progress/safety report to the REC and R&D.

9. STATISTICS

9.1 Description of Statistical Methods

A single proportion test will be applied to the primary outcome measure (see Section 6.2.1), using a reference proportion of 49 in 50. This is derived from a clinical estimate of the threshold for acceptable performance of the headgear being where the resulting endoscopy image is not sufficiently clear and stable in no more than 1 in 50 cases.

The secondary outcome measures (see Section 6.2.2) will be used as follows:

- The device usability and tolerability ratings will be used to support the risk/benefit ratio assessment of the device.
- Device usability and tolerability subjective feedback will be used to inform and prioritise how residual risks associated with usability and tolerability can be reduced.

9.2 The Number of Participants

The number of participants is limited to 30 for practical reasons, based on the expected rate that participants can be recruited.

The following rationale was applied to determine this as an acceptable number of samples:

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[4] https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/, accessed 16/Aug/2021

- This is a Class I (MDD), low-risk device, and risk management according to ISO 14971 has been used to predict a favourable overall risk/benefit ratio.
- Bench testing has been carried out to verify that the design meets the specifications.
- Limited validation of the headgear has been carried out to partially show that the device is fit for purpose. This included testing on humans but without the endoscope inserted into them. The results demonstrated to a large extent that the design is safe and effective.

9.3 The Level of Statistical Significance

A conservative level of significance of p=0.01 will be used to control the false discovery rate, due to the expected small limiting sample size (Harrell, 2015).

9.4 Criteria for the Termination of the Trial

The trial will be terminated in the event of any device-related SAE, SADE or USADE.

9.5 Procedure for Accounting for Missing, Unused, and Spurious Data

If the data is missing completely at random, and the fraction of missing data is no larger than 5%, then the missing data will be ignored in the analysis. If the data is missing at random, deletion is not a viable strategy, so imputation procedures will be applied to avoid biased estimates (Harrell, 2015).

9.6 Procedure for Reporting any Deviation(s) from the Original Statistical Plan

Any significant deviations from the statistical plan will be notified to the study sponsor.

9.7 Inclusion in Analysis

All eligible participants will be included in analysis.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

11. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, ICH GCP, BS EN ISO 14155, other relevant regulations and standard operating procedures.

Regular monitoring will be performed according to ICH GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

12. ETHICS

12.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

12.2 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice E6 (R2).

12.3 Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate REC, Health Research Authority and host institution(s) for written approval. Local capacity and capability approval will be sought from each participating NHS organisation.

A letter of no objection from the MHRA is not required as this is not a clinical investigation of a device intended to be UKCA/CE-marked, or commercialised.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

12.4 Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained, and all documents will be stored securely and only accessible by trial staff and authorised personnel. All paper documentation and participant identifiable data will be securely held in a locked drawer in the Voice clinic room, Broadgreen Hospital. This includes the consent forms, CRFs, and the participant list in an enrolment log. The participants will be identified only by participant's ID number on the CRF.

Pseudonymised electronic data will be held by Medical Physics and Clinical Engineering for analysis. The data for analysis will be held on secure, password protected and firewalled

network facilities provided by the department. Security arrangements include nightly backups and access controls to restrict access to those who need it.

The Chief Investigator will preserve the confidentiality of participants taking part in the study and will abide by the Data Protection Act 2018 and the UK GDPR as amended from time to time, any successor legislation in the UK and any other directly applicable regulation relating to data protection and privacy.

12.5 Other Ethical Considerations

There are no other ethical considerations.

13. DATA HANDLING AND RECORD KEEPING

The data is recorded on a hard copy of the CRF. A copy of this is given to the Chief Investigator for analysis.

A participant list is held by the Principal Investigator in an enrolment log to identify participants. The participants will be identified by a study specific participants number. The participant numbers will be prefixed with the letter 'H', and participants will be allocated a participant number incrementally starting at 'H1'. The name and any other identifying detail will NOT be included in any study data electronic file.

Following analysis, and within 12 months of the end of the study, electronic data will be anonymised and archived as described in Section 17.

14. FINANCING AND INSURANCE

LUHFT will act as Sponsor for this study. It is recognised that as an employee of LUHFT the Chief Investigator has been delegated specific duties, as detailed in the Sponsorship Approval letter.

NHS bodies are legally liable for the negligent acts and omissions of their employees. If a participant is harmed whilst taking part in a clinical trial as a result of negligence on the part of a member of the study team, this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. LUHFT, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered.

15. END OF STUDY DEFINITION

The study will formally end when the data collection has been completed from the last participant and data analysis is complete.

The study will be ended prematurely by the CI in the following cases:

- A SADE or USADE occurs;
- A DD is identified that might have led to a SADE if suitable action had not been taken, intervention had not been made or if circumstances had been less fortunate;
- Emergent information about the device risk causes the risk/benefit evaluation to become unfavourable.

16. PUBLICATION POLICY

An internal report will be produced detailing the findings from the study in the form of a clinical evaluation in line with MEDDEV 2.7/1 Clinical Evaluation: A Guide for Manufacturers. The study will also be used to update the Risk Log for the device.

Although the main reason for this Study is it to enable LUHFT to provide an additional service for patients, publication in a peer reviewed scientific journal or as a report on our website will be considered to disseminate the findings of this study to interested parties.

Authors will be defined as those who have made:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; **AND**
- Drafting the work or revising it critically for important intellectual content; **AND**
- Final approval of the version to be published; **AND**
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Contributors who have contributed materially to the paper but whose contributions do not justify authorship will be described clearly in acknowledgements.

17. ARCHIVING

All appropriate documentation and anonymised participant data will be archived by the Chief Investigator and stored securely behind a firewall in Medical Physics & Clinical Engineering for a minimum of 15 years after the completion of the study in accordance with the Sponsor

archiving SOP. Access to the archived data will be restricted to those involved in research within Medical Physics & Clinical Engineering.

18. REFERENCES

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