Evaluating the Therapeutic Use of a Vibratory Positive Expiratory Pressure Device (Acapella® Choice) in the Treatment of Pathological Voice - A Feasibility Study

Evaluating the Feasibility of Acapella® Choice as a Dysphonia Treatment

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Supported by:
Smiths Medical,
6000 Nathan Lane North
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USA

Sponsored by:
University College London Hospitals NHS Foundation Trust (UCLH)

Protocol version number and date: Version 2, 15/09/2020

R&D / Sponsor Reference Number(s): 18/0434

Study Registration Number:
18/0434

PROTOCOL VERSIONS

Version Stage	Versions No	Version Date	Protocol updated & finalised by;	Appendix No detail the reason(s) for the protocol update
Current	Version 2	15/09/2020	Brian Saccente-Kennedy, Specialist SLT	Following Substantial Amendment 1
Previous	Version 1	18/01/2018	Brian Saccente-Kennedy, Specialist SLT	

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 15/09/2020

Print Name(in full): Brian Saccente-Kennedy CertMRCSLT

Position: Specialist Speech and Language Therapist

On behalf of the Study Sponsor:

Signature:..... **.....**
Date.....22./10...../..2020.....

Print Name Pushpsen Joshi

Research Governance Manager

STUDY SUMMARY

Identifiers	
IRAS Number	251733
REC Reference No	
Sponsor Reference No	18/0434
Other research reference number(s) (if applicable)	
Full (Scientific) title	Evaluating the Impact of a Vibratory Positive Expiratory Pressure Device (Acapella®Choice) on Pathological Voice - A Feasibility Study
Health condition(s) or problem(s) studied	Dysphonia (arising from muscle tension dysphonia, presbylaryngis and vocal fold palsy)
Study Type i.e. Cohort etc	Feasibility study
Target sample size	30 (10 of each condition)
STUDY TIMELINES	
Study Duration/length	18 Months
Expected Start Date	January 2020
End of Study definition and anticipated date	When 30 participants have been recruited and have taken part, or 18 months have elapsed, whichever comes first.
Key Study milestones	Securing of funding, JRO submission, first patient recruitment, study close.
FUNDING & Other	
Funding	Sabah Mujeebuddin, Clinical Research Specialist, CHEM **Smith's Medical,** 6000 Nathan Lane North, Plymouth, MN 55442 USA
Other support	N/A
STORAGE of SAMPLES (if applicable)	
Data collected / Storage	N/A
KEY STUDY CONTACTS	Full contact details including phone, email and fax numbers
Chief Investigator	Brian Saccente-Kennedy Brian.saccente-kennedy@nhs.net Tel/Fax: 020 3456 5180

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.

PRINCIPLE INVESTIGATOR (PI): The person who takes overall responsibility for the design, conduct and reporting of a study, ensuring that the study is conducted as per the approved study protocol, and report/notify the relevant parties of any breaches or incidents related to the study.

The PI 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 Principle Investigator is responsible for submission of annual reports as required. The Principle 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 Principle Investigator will submit a final report with the results, including any publications/abstracts to the REC.

KEY WORDS

Semi-occluded vocal tract exercise, positive expiratory pressure, tube phonation, Acapella, voice therapy.

LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
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
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
SOP	Standard Operating Procedure
SSI	Site Specific Information
TMF	Trial Master File

CONTENTS

1. INTRODUCTION

This feasibility study is the natural extension of our recently completed study (R&D 16/0242) which assessed how the use of an Acapella Choice (Smiths Medical) positive expiratory pressure (PEP) device as a semi-occluded vocal tract exercise (SOVTE) impacted acoustic, electroglottographic and aerodynamic measures of the voice in a group of normophonic volunteers. In that study, Acapella Choice was found to offer significantly greater oscillating intraoral pressures than techniques in current clinical practice and was found to have measurable benefits in terms of producing a louder and more economical voice. It offered the largest oscillating pressures, likened to a 'massage' of the vocal organs, giving it great therapeutic promise for patients with excess vocal tract tension.

We seek in this study to evaluate the immediate effects of Acapella Choice as a voice exercise in patients with Muscle Tension Dysphonia, Presbylaryngis and Vocal Fold Palsy, and compare this to our currently-used technique of phonation into a tube held under water (henceforward referred to as "Tube"). Patients will be recruited from four weekly Voice Clinics held at the Royal National Throat Nose and Ear Hospital where their diagnosis will be confirmed. They will be invited to attend a single experimental session during which time they will exercise both with Acapella Choice and with Tube. Baseline and outcome voice measures will be taken and a short questionnaire will be completed, eliciting perceptions of the two exercises and any changes which were felt to have resulted from them.

Our previous work suggests that Acapella Choice as a SOVTE may offer significant clinical benefits in terms of improved efficacy of therapy. We suggest that it also offers patients a more convenient and user-friendly form of exercise which may well improve compliance and result in better outcomes.

2. BACKGROUND AND RATIONALE

The therapeutic use of a semi-occluded vocal tract has a very long history and includes time-honoured techniques such as voiced fricatives, lip trills, tongue trills and even humming. Despite been used for generations by singers, the benefits to the voice were until recently purely anecdotal and their scientific basis unexplored. In the early 2000s, Prof Ingo Titze undertook a scientific investigation of the benefits of narrowing the vocal tract, specifically with thin flow-resistant straws. His work[1] concluded that benefits to the voice are derived from a heightened interaction of the vibration source (vocal folds) with the vocal tract to make the voice more economic and to reduce collision forces of the vocal fold tissues. A good review of the phenomenon can be found in Titze 2006[2].

Another form of SOVTE, initially introduced in Finland in the 1960s, involved phonation through glass tubes in air and glass tubes submerged in water. First written about by Dr Antti Sovijärvi[3], it was little used outside of Finland until it was introduced in the English-speaking literature in the mid-2000s[4]. By submerging the distal end of a tube under water, bubbling is generated, adding an oscillatory component to the static intraoral pressure[5–8]. This pressure modulation by water bubbling has been described as producing a 'massage effect'[4–6,9–11] on the laryngeal muscles that supposedly counteracts harmful maladaptation such as hyperfunctional phonation. This technique is one of the most commonly used by our department at the Royal National Throat, Nose and Ear Hospital.

Clinical experience has shown that many dysphonic patients respond quite well to a form of SOVTE and it comprises a key part of therapeutic intervention. There is a growing body of recent literature which is investigating what effect these exercises have on the phonation of both healthy subjects and those with voice disorders[7,10–18]. Various studies have shown that SOVTEs induce a lower laryngeal position[7,19] (often a marker of a deconstricted vocal tract), a firmer closure at the velopharyngeal port[20], a narrowed epilarynx and widened pharynx[19] which contribute to richer harmonics, improved vocal fold closure[2] - all leading to improved voice quality and laryngeal efficiency.

Vibratory PEP devices, such as Acapella Choice, are traditionally used to mobilize secretions in the treatment of excessive sputum or secretion retention in conditions such as cystic fibrosis and neurogenic diseases[21,22]. PEP devices are usually composed of a mouthpiece attached to a tube with a distal oscillatory flap that closes and opens with airflow, producing an oscillatory pressure within the airways. They aim to match the frequency of vibration of the ciliary epithelium in the lungs, hence promoting the expectoration of secretions.

A practical limitation for implementing tube-in-water voice exercises is the obvious requirement of an accessible water container. PEP, which offers an alternative source of oscillatory pressure without such requirements, might therefore have potential as a form of SOVTE. It was for this reason that we sought to investigate its potential in voice therapy in our previous study.

Our previous study was the first to investigate the use of a PEP device in voice rehabilitation. We found that Acapella® offered significantly greater oscillatory and static pressures than was obtainable from tube-in-water therapy and was the only exercise to create a significant change in loudness alongside improved vocal economy. As this study involved only participants with healthy voice, it remains to be seen how different categories of pathological voice, i.e. hyperfunctional and hypofunctional, would respond to exercising with Acapella®.

3. OBJECTIVES

3.1. Primary Objective

To determine what impact the use of an Acapella Choice device has on the voices of people with voice disorders when it is used as a form of semi-occluded vocal tract exercise.

3.2. Secondary Objectives

To identify whether this patient group is able to make use of Acapella Choice for this purpose

To identify if this intervention can be incorporated into the standard patient clinical pathway

To identify if sufficient subjects can be recruited and retained

To identify sample sizes for possible future research

4. STUDY DESIGN

This is a feasibility study using a 'before and after' design to test the immediate effects of exercising with Acapella Choice in comparison to the immediate effects of exercising with Tube. Dysphonic subjects will be recruited from referrals received from four RNTNE-based voice clinics with an endoscopically-confirmed diagnosis of muscle tension dysphonia (MTD), presbylaryngis (age-related vocal fold atrophy) or vocal fold palsy. They will attend only one research session which will last approximately one hour.

The aim is to recruit ten subjects from each diagnosis for a total of 30 patients. As this is a feasibility study, a sample size calculation has not been performed. Instead, the target number for recruitment is instead informed by a recent audit of referrals to the department.

5. STUDY SCHEDULE

Enrolment will begin from day one of the study. Prospective participants will be identified by the Speech Therapist in attendance at voice clinics held at the Royal National Throat Nose and Ear Hospital. The therapist will briefly explain the study, give the patient and information sheet, and get consent for the PI to contact them over the following week to carry out a telephone screening of their eligibility.

Following successful screening by the PI, the participant will be given an appointment to attend an approximately one hour long research session where the interventions will be carried out and data collected. This single session will conclude the participant's involvement in the study, and they will return to their ordinary clinical pathway, awaiting commencement of their Speech Therapy input, as indicated. There will be no study follow-up for participants.

A participant may withdraw at any time and their normal clinical pathway from referral to treatment will remain unaffected.

The end of the study will be reached as soon as the target number of participants has been recruited, or eighteen months has elapsed from the commencement of the study, whichever comes first.

6. CONSENT

Written informed consent will be obtained at the beginning of the study visit. By this point the participant will have already received and had a chance to read the participant information sheet and ask any questions during their recruitment telephone conversation with the PI.

7. ELIGIBILITY CRITERIA

7.1. Inclusion Criteria

- Able to understand written English without the need for an interpreter,
- No diagnosed communication impairment
- Endoscopically confirmed primary ENT diagnosis of either:
    1. muscle tension dysphonia (with no laryngeal abnormality),
    2. Vocal fold palsy
    3. Presbylaryngis.

7.2. Exclusion Criteria

- Under 18 years of age or over 90 years of age.
- Previous SLT input
- Any of the following possible contraindications for PEP therapy:
    - Inability to tolerate increased work of breathing,
    - ICP (intracranial pressure) > 20mm Hg,
    - Recent facial/oral/skull surgery or trauma,
    - Oesophageal surgery,
    - Untreated pneumothorax,
    - Known or suspected tympanic membrane rupture/other middle ear pathology,
    - Haemodynamic instability,
    - Acute sinusitis,
    - Epistaxis,
    - Active haemoptysis,
    - Nausea

8. RECRUITMENT

Whenever possible, participants are to be preferentially recruited from within joint- or Speech Therapy-led voice clinics (four in total each week). In this way, a member of the Speech Therapy team who has knowledge of the study and the inclusion criteria can assist in making a preliminary assessment of the participant's suitability for the study. The participant will then be given a brief verbal explanation of the study and a participant information sheet to take away with them.

As a result of significantly reduced patient numbers in joint voice clinics, and the temporary halting of Speech Therapy-led voice clinics (both as a result of Covid-19 precautions), participants may *alternatively* be identified from the waiting list of patients referred to ENT Speech Therapy by an ENT consultant but who have not yet received voice therapy. In this way, the PI will be able to review the patient's video recorded laryngeal exam and make an assessment of their suitability for the study. Those who are suitable will be contacted via telephone and given a brief verbal explanation of the study and a participant information sheet put in the post for those who are interested in finding out more.

The prospective participant will then be telephoned by the PI during the following week. The PI will ask over the telephone whether they have any of the contraindications for PEP which would result in their being deemed unsuitable for inclusion in the study and will answer any

questions the participant might have. Should they meet all inclusion criteria, the PI will then set up a day and time to come in, give informed consent, and participate in a single research session lasting around one hour. Should they not be eligible for inclusion in the study, this will be documented in the study file's Screening Log.

This research session will complete the subject's involvement in the study, and they will then be returned to the normal clinical pathway and receive Speech Therapy input as indicated and in a timely fashion dependent on their place on the waiting list. Participants will be compensated for their time with a £10 gift voucher and their travel expenses will be reimbursed up to a maximum of £12.50 (London Zone 1-6 daily cap) providing presentation of valid receipts.

9. STATISTICAL METHODS

As this is a feasibility study and this is the first time that this particular exercise has been trialled in pathological voice, effect sizes are as yet unknown. The decision to recruit 10 participants of each voice type was informed by a recent audit of departmental referrals (January 2015 to July 2017). Over this period, we received an average of 57 referrals per month. Monthly referrals for MTD account for 15.8% of that total (9), referrals for vocal fold palsy account for 6.5% (4) and referrals for presbylaryngis account for 5.9% (3). It was felt that 10 of each group was reasonable to recruit within the planned timescale of the study (initially, 12 months, but owing to a significant drop in throughput of patients in voice clinics as a result of Covid-19, this timescale has been extended to 18 months), large enough to inform about the practicalities of recruiting for a larger future study and large enough to provide some indication of the effects of each treatment on baseline variables.

Despite it being unclear what effects will be seen in these clinical populations, our previous pilot using normophonic volunteers was able to identify statistically significant change in sound pressure level (SPL) and mean flow during voicing, both biologically relevant changes for voice production. For this study, descriptive statistics will be used and will include box plots, means/medians, standard error and tests of significant differences between groups and exercises will be carried out using ANOVAs. Baseline data for consideration will include expert-rated perceptual, acoustic, aerodynamic and electroglottographic measures of the voice.

Questionnaire data will also be collected and will be analysed for pre-post changes in self-rated voice quality and ease of voice production. Views on the exercises (i.e. ease of use, portability, likelihood of carrying out task if it were given in a therapy programme) will also be compared between exercises and between groups.

10. PATIENT AND PUBLIC INVOLVEMENT (PPI)

Patients are the participants (research subjects) in this study, and as such, are a key part of the research process. Not only will they participate in the two interventions being investigated, but their opinions of the recruitment process and experience of data collection will be sought so as to inform a future and larger study. It is hoped that in this way we will be able to ensure the smoothest and optimal patient experience for future studies.

However, in terms of the present proposed study, as it is a rather small scale feasibility study we do not anticipate there will be any need for patient or public involvement in the research management, research undertaking, analysis or finding dissemination. However, we did seek

the input of members of the public (voice clinic attendees) to help us hone the clarity of our patient information sheets and settle on the amount of participant compensation (gift certificates and travel costs). As a result of their input, the information sheets were revised and compensation levels increased.

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 a grant from Smith's Medical in the amount of £14,257 (inclusive of one year of 0.2 WTE backfill of clinician time, equipment upgrade, consumables, participant incentive voucher purchase, travel and accommodation at international conference). Smith's Medical will also be supplying twenty-six (26) Acapella Choice Devices to be used by the participants of this study (to supplement the four devices which the department already holds in stock).

All instrumental assessment to be carried out using equipment already present in the Royal National Throat, Nose and Ear Hospital's Voice Lab, namely a PENTAX Computerised Speech Lab (Model 4150), EGG Module (Model 6103) and Phonatory Aerodynamic System (Model 6600).

12. DATA HANDLING AND MANAGEMENT

The study is compliant with the requirements of General Data Protection Regulation (2016/679) and the Data Protection Act (2018). All investigators and study site staff will comply with the requirements of the General Data Protection Regulation (2016/679) with regards to the collection, storage, processing and disclosure of personal information, and will uphold the Act's core principles. UCLH is the data controller; the UCLH Data Protection Officer can be contacted on deborah.dillon2@nhs.net The data processors are UCLH. The study will be collecting the following personal data:

- Basic demographic and diagnosis data drawn from medical and electronic records, (i.e. age, gender, findings of ENT exam)

Experimental data, which is non-identifiable, that will be collected in the course of the research include:

- Electronic voice recordings, electronic intraoral pressure recordings, electroglottographic recordings and patient questionnaire data.

Electronic files will be anonymised with participant codes and held on the hospital shared drive, questionnaires will be codified into an electronic spreadsheet and the hard copies stored in the study file, which is maintained in the RNTNE SLT (ENT) Department. The study file will contain a record of all written consents and a list of participant codes; the study file will not leave the premises.

Instrumental data, anonymised by participant code, will occasionally be electronically transferred to the study's co-author, Dr Pedro Amarante Andrade (Visiting Researcher, Academy of Performing Arts in Prague, Malá Strana, Czechia), for specialist analysis. This will not include personally identifiable data.

13. PEER AND REGULATORY REVIEW

The study has been peer reviewed in accordance with the requirements outlined by UCLH.

This study has been peer reviewed within UCLH and by an independent and relevant peer reviewer on 13th November 2018 and 21st November 2018, respectively. The Sponsor has accepted these reviews as adequate evidence of peer review.

14. ASSESSMENT AND MANAGEMENT OF RISK

The manufacturer cautions against using excessive pulmonary pressures with the Acapella Choice (i.e. in excess of 20 cmH_2O) as this might lead to an adverse effect in those who are sensitive to increased transpulmonary pressures. The manufacturer advises that adverse effects might include:

- Increased work of breathing that might lead to hyperventilation
- Increased cranial pressure
- Cardiovascular compromise (myocardial ischaemia, decreased venous return)
- Air swallowing with increased likelihood of vomiting and aspiration
- Claustrophobia
- Pulmonary barotraumas

In our recent pilot study involving only normal and healthy volunteers, not one of the 22 participants exceeded this level of 'excessive' pressure. During the pilot, the mean pressure during Acapella exercise was in fact only 6.22 cmH_2O, (range 3.98-16.75 cmH_2O). As the participants in this study are more likely to have lower pulmonary pressures (owing to an expected higher mean age), it seems unlikely that this pressure will be exceeded. Additionally, the list of adverse effects is indeed related to the list of contraindications for PEP exercising (i.e. those who are sensitive to increased transpulmonary pressure), and these are included in our exclusion criteria. Furthermore, the experimental protocol involves live monitoring intraoral pressure during exercising. As such, the task will be aborted if this upper pressure limit is being reached.

The other task examined in this study ("Tube") is part of the normal input of our department, is limited by design to 5 cmH_2O intraoral pressure and has never resulted in the need to report an adverse effect in the many years of its therapeutic use at the Royal National Throat, Nose and Ear Hospital.

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**, ● 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 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 the information about the procedure listed in the manual of operation **or clearly defined in this protocol.**
Unexpected	An adverse event which is not consistent with the information about the procedure listed in the manual of operation* **or clearly defined in this protocol.**

* this includes listed events that are more frequently reported or more severe than previously reported

15.3. Recording adverse events

All adverse events will be recorded in the medical records in the first instance.

All Adverse events 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, including dates as appropriate.

15.4. Procedures for recording and reporting Serious Adverse Events

All serious adverse events will be recorded in the medical records and 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 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.

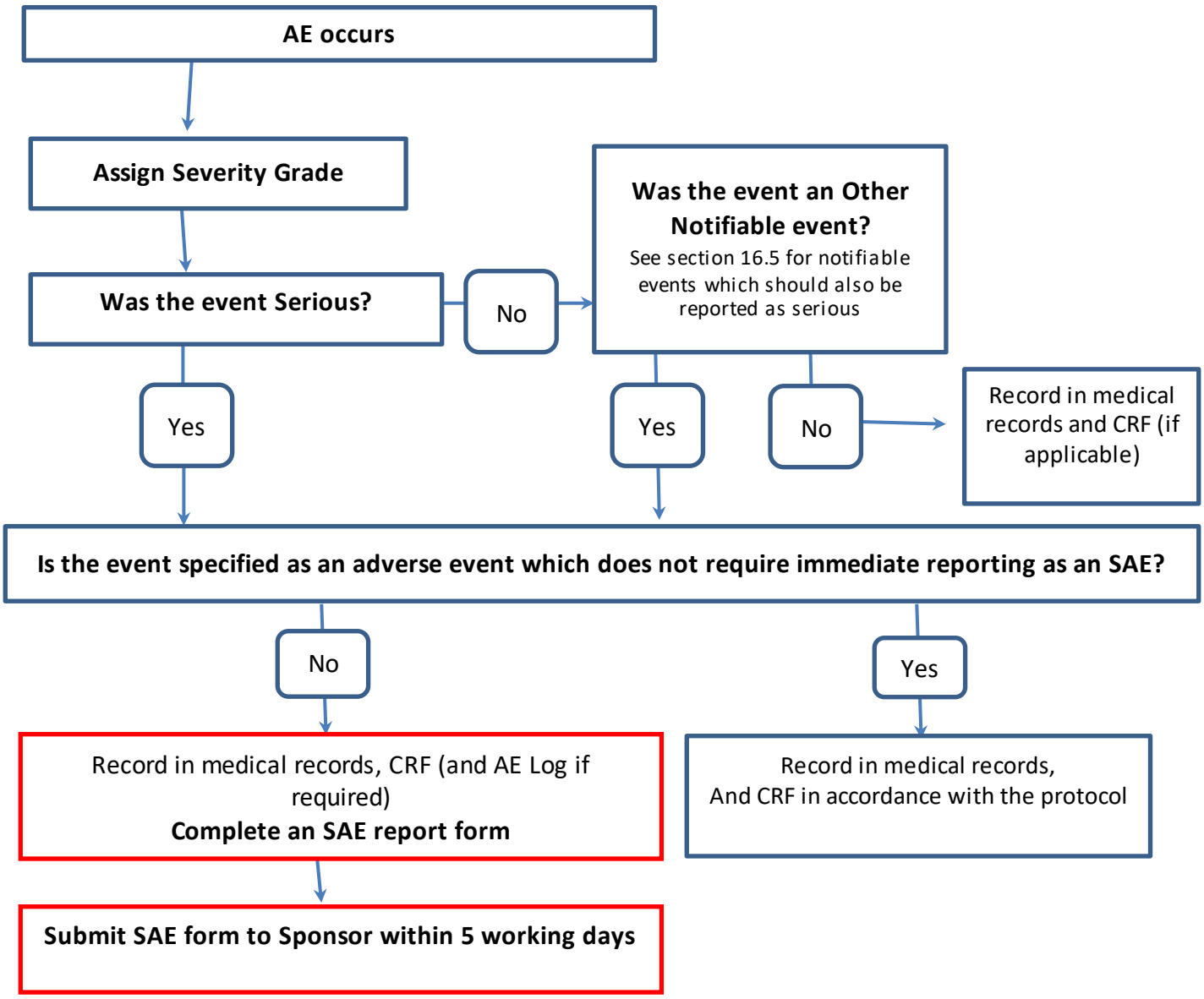
Where the event is unexpected and thought to be related to the procedure this must be reported by the Investigator to the Health Research Authority within 15 days.

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



15.5. Reporting Urgent Safety Measures

If any urgent safety measures are taken the 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.

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

15.7.Reporting incidents involving a medical device

Any adverse incident involving a medical device should be reported to the manufacturer of the device.

This is especially important where the incident has led to or, was it to occur again could lead to an event classified as serious (see section 9.1 for definition of SAE). Other minor safety or quality problems should be reported along with incidents that appear to be caused by human error.

All adverse incidents must be reported to Smith's Medical International via globalcomplaints@smiths-medical.com.

Incidents should be reported within 24 hours.

15.8.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

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

The PI will inform the sponsor should he/she have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

17. TRAINING

The Principle Investigator will review and provide assurances of the training and experience of all staff working on this study. Appropriate training records will be maintained in the study files

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. Each participating site agrees that by giving approval to conduct the study at its respective site, it is also agreeing to effectively assign all such intellectual property rights ("IPR") to UCLH and to disclose all such know-how to UCLH with the understanding that they may use know-know gained during the study in clinical services and teaching to the extent that such use does not result in disclosure of UCLH confidential information or infringement of UCLH IPR.

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 and each participating site recognise that there is an obligation to archive study-related documents at the end of the study (as such end is defined within this protocol). The study master file will be archived at UCLH 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

It is anticipated that the results for this study will be disseminated via publication in a peer-reviewed journal, such as the Journal of Voice.

22. REFERENCES

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