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| **PCH-CU: Description of Primary Cough Headache in a Cough Unit: A prospective study.**  |
| **Sponsor:** | King’s College Hospital NHS Foundation Trust (KCH)  |
| **Funder (s):** | *NIHR BRC grant – Pain theme* |
| **IRAS Reference** | 256341 |

**Protocol Version and Date Version 2.2, 28 January 2019**

**KEY ROLES AND RESPONSIBILITIES**

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

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

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

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

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

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

**OTHER: NA**

**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 Governance 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 this research 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:**

**Print Name:** *PETER J. GOADSBY*

**Position:** *PROFESSOR OF NEUROLOGY*

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**KEY WORDS**

Cough headache, Cough, Valsalva.

**LIST OF ABBREVIATIONS**

|  |  |
| --- | --- |
| AE | Adverse Event |
| ARCAG | Adverse ReactionConfidential Advisory Group |
| CI | Chief Investigator |
| CRF | Case Report Form |
| DMC | Data Monitoring Committee |
| GAfREC | Governance Arrangement for NHS Research Ethics |
| HRA | Health Research Authority |
| HTA | Human Tissue Authority |
| ICF | Informed Consent Form |
| ISRCTN | International Standard Randomised Controlled Studies Number |
| PI | Principal Investigator |
| PIS | Participant Information Sheet |
| QA | Quality Assurance |
| QC | Quality Control |
| REC | Research Ethics committee |
| SAR | Serious Adverse Reaction |
| SAE | Serious Adverse Event |
| SDV | Source Data Verification |
| SOP | Standard Operating Procedure |
| TMFCTFPCH  | Trial Master FileClinical Trial FacilityPrimary Cough Headache |
| PII | Personal identifiable information  |

CU Cough Unit

# Trial personnel

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**STUDY SUMMARY**

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| **STUDY OVERVIEW** |
| Full title | PCH-CU: Description of Primary Cough Headache in a Cough Unit: A prospective study.  |
| Objectives | To better describe headache features and investigate the prevalence and possible comorbidities of Primary Cough Headache in patients attending the Cough Unit Consultation.  |
| Type of trial | Cross-sectional study.  |
| Health condition(s) or problem(s) studied | Cough headache. |
| Target sample size | 50 expected participants (500 patients to be screened). |
| Trial design and methods | The study is an observational design and consists of one visit; Previously, a pre-screening questionnaire performed at the cough clinic will determine potential eligibility. Study visit: consent will be sought and, after screening, eligible participants will go through a semi-structured interview in which general medical history and features of headache will be assessed. Neurological examination will be performed as well as modified a Valsalva Test.  |
| Trial duration per participant: | All participants will complete the trial once the study visit has been completed.  |
| Main inclusion/exclusion criteria: | Male and female patients with a diagnosis of Cough headache aged between 18-80 years will be enrolled. Participants must be willing and able to comply with scheduled visit and neurological exam.Subjects with history of brain haemorrhage, brain tumour, brain aneurism or any brain mass will be excluded. |
| Statistical methodology and analysis: | Description statistics: Proportions, means, medians; Students t-test, Pearson Chi squared, and Pearson correlation coefficient.  |
| **STUDY TIMELINES** |
| Study Duration/length | 12-18 months |
| Expected Start Date | July 2019 |
| End of Study definition and anticipated date | Study end: All participants complete the study visit (unless withdrawn). Anticipated date: December 2019 |
| Key Study milestones  | REC submission September 2018; FPFV October 2018 |

# INTRODUCTION

Since it was first described by Sir Charles Simonds in 1956 (1), Primary Cough Headache (PCH) has been scarcely documented in the literature. Only some studies published by Ozge et al. (2), Pascual et al. (3,4,5) and Chen et al. (6) (which reported 74 patients), have led to the description of the main features of this entity and the diagnostic criteria (ICH-III) (7). According to the latter, it is a short-lasting (1 second to 2 hours), sudden headache, brought on by and occurring only in association with coughing, straining and/ or other Valsalva manoeuvre. Its prevalence is thought to be around 1%, although it could affect up to 20% of patients in Cough Units (2). Pathophysiology is still uncertain, although different theories have been proposed (5, 8). By recruiting the highest number of patients to date, this study aims to provide a better description of the PCH features and its possible relationship with other comorbidities.

# BACKGROUND AND RATIONALE

According to the current available data, PCH occurs mainly in subjects over the age of 40 years, being the mean age of onset 67 years (4). A male predominance has been pointed, although the male/female ratio changes dramatically among series. Furthermore, it seems to be an episodic disease as it normally lasts less than 2 years. Pain is usually localized bilaterally, with a major involvement of the occipital region. Pain quality, however, has been described as sharp, stabbing, splitting, explosive, electrical, pressing, dull or even pulsatile. Precipitants may include coughing, sneezing, nose blowing, laughing, crying, singing, lifting a weight, straining at stool, and stooping (4). Nevertheless, they should not include sustained physical exercise which would be typical of exertional headache (7). Regarding the headache associated features, nausea, dizziness and photo/photophobia have been documented in a very little proportion of patients, being these, vertigo, ataxia and syncope, red flags indicating a probable secondary origin.

In this context, differential diagnosis with secondary or symptomatic cough headache is crucial. The most common reported cause is Chiari type 1 malformation, although any posterior fossa lesion could cause the symptoms as well as syringomyelia, platybasia, obstructive hydrocephalus, subdural hematoma, sphenoid sinusitis, spontaneous intracranial hypotension, brain aneurysm and even carotid artery disease (10). Overall, it is considered that almost 50% of cough headaches are symptomatic. However, the only published study in cough patients found 3/32 (9%) secondary headaches (all of them due to Arnold Chiari malformation) (2).

A 16-patient study showed that a modified Valsalva manoeuvre (exhalation into the spigot of an aneroid sphygmomanometer to a pressure of 60 mm Hg and maintain this for 10 seconds) was capable of distinguishing primary from secondary headache (9). According to this result, the authors hypothesized that a transient increase in intracranial pressure during exertion due to obstruction to normal CSF dynamics should explain secondary Cough headache. Conversely, they stated PCH could be caused through congestion of the orbital venous plexus (8) in the presence of jugular venous incompetence and a reduced threshold for trigeminal sensory activation. On the other hand, it is argued that a relative obstruction of CSF flow could take place, following research by Chen et al. (11), who described a more crowded posterior fossa in PCH patients.

PCH may respond to Indomethacin (50-150 mg daily) which has also been attributed to its carbonic anhydrase inhibitor property, leading to decreased intracranial pressure.

Knowledge on the clinical aspects of this disorder is a necessary step towards the understanding of the pathophysiology and subsequent development of targeted therapies, hence, a better description of PCH patients is required.

# OBJECTIVES

## Primary Objective

* To investigate the clinical features and prevalence of Cough headache in patients attending a Cough Unit and, potentially, to determine differences between primary and secondary Cough headache.

## Secondary Objectives

* To find specific comorbidities related to Cough headache.
* To investigate the use of opioids and other drugs in Cough patients and its possible relationship with the development of chronic headache.
* To test the utility of the modified Valsalva manoeuvre in these patients.

# STUDY DESIGN

The study design consists of a cross-sectional study of one group of patients. Consecutive patients attending the Cough Clinic will be asked to complete a pre-screening (only two questions, asking for the presence of headache and headache after coughing). The focus of pre-screening is to find potentially eligible patients. Patients will be given the PIS at the clinic along with detailed information on the project, if required so. Patients will be given the research team contact details so that they could contact us, should they be interested in participating.

Patients who contact the research team will be asked to complete the Study visit at the Clinical Research Facility, King’s College Hospital. This entails the standard informed consent process, screening and inclusion/exclusion criteria to confirm eligibility. Following this, eligible participants will complete undergo a semi-structured interview, physical/ neurological examination and the modified Valsalva manoeuvre (see the flow chart below).

In those eligible (cough headache) patients with no previous neuroimaging performed (either brain MRI or brain CT scan) in which physical/ neurological examination show any abnormality, a referral will be made to the KCH NHS headache clinic for the arrangement of a cranio-cervical MRI.

### Pre-screening

The clinical team at the KCH cough clinic conduct a questionnaire for as part of standard clinical care. The clinical team will speak with patients during their clinic appointment who answer “Yes” to the questions “Have you had any form of headache in the last one year?” and “Do you have headache after coughing?”, and will ask if the patient is interested in research. Patients who are interested will be given the participant information sheet (PIS) and the research team contact details.

### Study visit

The investigator (or an appropriate delegate at the investigator site) will obtain Informed Consent from each subject in accordance with the Patient Information Sheet and Patient Informed Consent Form.

Subjects will be screened via oral questioning and it will be confirmed that they meet the subject selection criteria for the trial. Eligible participants will complete a detailed semi-structured interview, which will include:

* Age and gender.
* Complete medical history, including confirmation of Cough severity, previous infections, sleep abnormality, respiratory diseases (asthma, COPD…) and detailed history taking.
* Complete history of all prescription or non-prescription drugs, opioids, angiotensin converter enzyme inhibitor (ACEI).
* History of drug, alcohol and tobacco use.
* Three item- ID-migraine.
* Headache history: Frequency, persistence, onset, duration, location, age of onset, quality, associated features, cranial autonomic symptoms, aura, premonitory or postdrome and precipitants/ triggers.
* Previous infections. Sleep abnormality.
* Family history.

Subjects will undergo the following procedures:

* Measurement of height, weight, sitting blood pressure and pulse rate.
* Complete physical and neurological examination including eye fundus. Specifically searching for ataxia/ unsteadiness, dysdiadochokinesia, dysmetria and nystagmus.
* Perform modified Valsalva Test: exhale into the spigot of the rubber connecting tube of an aneroid sphygmomanometer to a pressure of 60 mm Hg and to maintain this for 10 seconds.
* Review of prior MRI exams or other neuroimaging studies. If no neuroimaging study has been performed and any abnormality is shown on the physical exam, a referral will be made to the KCH NHS headache clinic for the arrangement of a cranio-cervical MRI.
* Review of prior/concomitant medications
* Review of changes in the subject’s medical history since screening.

### Follow-up

Primary cough headache is normally a self-limited disease that lasts for no more than 2 years (5). An oral indomethacin trial may be recommended if there is no contraindication, as follows:

* Indomethacin 25mg three times daily for five days, followed by 50mg three times daily for five days, followed by 75mg three times daily for two weeks. If attacks are suppressed, further dose escalation is not necessary. We will recommend a proton pump inhibitor during this trial.

# STUDY SCHEDULE

Subjects will only be enrolled in the study once. Ten to fifteen patients a week will attend the Cough clinic. Initial pre-screening will include a simple questionnaire used as standard clinical care. Potentially eligible patients willing to participate will contact the research team and then proceed to the study visit. Cough headache patients will complete interview and procedures. At the end of the study visit the subjects will have completed the study. The investigator must be confident all eligibility criteria have been fulfilled for the subject may proceed to the study visit. The study team will have the possibility of re-contacting subjects who have taken part and completed the study, to offer a follow-up visit for eventual additional procedures. If procedures other than those conducted at the study visit are proposed, then a protocol and information sheet amendment will be submitted.

* Participant withdrawal criteria and procedures

A patient may discontinue participation in the study at any time for any reason (eg, consent withdrawn, or adverse event) without obligation to provide this reason to the investigator. The investigator and/or sponsor can withdraw a patient from the study at any time for any reason which prevents the safe execution of the protocol or which may invalidate data obtained from study procedures. In cases of withdrawal, participants will be asked whether data collected up to the date of withdrawal may be still be used in the analysis, this discussion must be recorded in the source documentation together with a reason for withdrawal if freely given. Withdrawal is immediate and absolute; an end of study visit is not required and will not be requested.

Participants may also withdraw their data from analysis at any time during or after the visit schedule is complete. In cases where data destruction is requested; all samples and data relating to the patient must be destroyed without delay. The only data to remain in the trial master file will be: subject number, reason for withdrawal/ data destruction (if applicable), and records of sample/ data destruction.

**Study schedule**

|  |  |  |
| --- | --- | --- |
| **Assessment** | **Measuring** | **Study visit** |
| Informed Consent Past medical historyHeadache historyCough history Clinical assessment Review of medications Review of previous exams Physical/ neurological examInclusion and exclusion criteria Adverse events  | Headache symptoms (features)Severity, respiratory history. Blood pressure, pulse rate.Prior and concomitant medicationNeuroimaging (MRI, CT).  | \*\*\* \*\* \*\*\* \* \*  |
| **Procedures** | **Comment** |  |
| Modified Valsalva test *a* |  | \* |

*a – Exhalation into the spigot of the rubber connecting tube of an aneroid sphygmomanometer to a pressure of 60 mm Hg and to maintain this for 10 seconds.*

# CONSENT

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures. In case of data transfer, appropriate standards of confidentiality and protection of subject personal data will be maintained.

The investigator will ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The informed consent form used in this study, and any changes made during the course of the study, will be approved by both the IRB/IEC before use. The investigator will retain the original of each subject's signed consent form.

Subjects will undergo the informed consent process with an investigator (or appropriately delegated study team member) during the study visit as described above.

# ELIGIBILITY CRITERIA

## Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrolment into the study:

1. Patients are capable of giving signed informed consent indicating that the subject (or a legally acceptable representative) has been informed of all pertinent aspects of the trial detailed in the patient information sheet (PIS), informed consent form (ICF), and in this protocol.
2. Subjects must be willing to receive a telephone call or travel to and from King’s College Hospital as preferred, during normal working hours.
3. Diagnosis of Primary Cough Headache (PCH) using criteria previously published (1).
4. Aged 18-80 years inclusive**.**
5. Willing and able to comply with scheduled visits and study procedures.

## Exclusion Criteria

Subjects presenting with any of the following will not be included in the study

1. Pregnancy or breastfeeding from consent until the end of study involvement.
2. History of psychosis, depression or psychological diseases either (a) requiring ongoing psychoactive drugs, or (b) that the Investigator has reason to believe will either affect the patient’s neural pathways or hinder the performance of the patient with regard to ability to successfully complete the tasks required of them according to the protocol.
3. History/ presence of cerebral haemorrhage, brain tumour, brain aneurism, cryptococosis or other brain mass lesion within the last 12 months.
4. Any other medical condition that in the opinion of the Investigator would make the subject unsuitable for the study.
5. Inclusion to another research study within the past 30 days.

# RECRUITMENT

Patients attending the King’s College Hospital Cough clinic will be approached by the clinical team and invited to take part in the research if they answer “Yes” to the questions “Have you had any form of headache in the last one year?” and “Do you have headache after coughing?”. Participants may also be identified from Professor Goadsby’s clinic at King’s College Hospital, in which case the above procedure will also apply.

The clinical team will give the PIS to patients and pass the telephone number and email address of the research team to contact us if interested. Upon contact, willing patients suitable for the study will be invited to the study visit at which point informed consent will be sought. The visit will be performed at the Clinical Trial Facility.

The study team reserve the right to invite further sites to partake and will submit an amendment should this eventuality arise.

# STATISTICAL METHODS

This is an exploratory study on a condition that has been scarcely described and characterized in the literature. With only one previous study on a Cough clinic showing a prevalence of Cough headache of 20%, 1000 to 750 subjects should be screened in this population to find 50 patients with PCH.

The analysis of the collected data will be analysed using STATA 12 for Mac/ SPSS 24 for Windows.

Description statistics including proportions, means, medians and ranges will be performed.

Normality will be tested using Shapiro-Wilk test. Analytical statistics, including Students t test, Pearson Chi squared, and Pearson correlation coefficient as well as the non-parametric versions if applicable (U of Mann-Whitney, and Spearman coefficient, respectively) will be performed. Correction for multiple comparisons shall be made.

The level of significance to be used in this Trial will assume a Type 1 error/ alpha of 0.05.

# FUNDING AND SUPPLY OF EQUIPMENT

The study funding has been reviewed by the KCH R&I Office, and deemed sufficient to cover the requirements of the study.

The research costs for the study will be supported by NIHR BRC grant – Pain theme.

# DATA HANDLING AND MANAGEMENT

Each patient will be assigned a study number. Personal Identifiable Information (PII) and medical records from participants recruited at the site (King’s College Hospital) will be de-identified and recorded on source documents created specifically for the study. Source documents from participants recruited at the site (King’s College Hospital) and consent forms will be stored in the Headache Group, Clinical Research Office, Welcome Foundation Building, Denmark Hill Campus, King’s College London. Access to this office is restricted and paperwork is stored in locked filing cabinets.

Source documentation collected will be stored as per local data protection standard operating procedures.

Clinical data from source documents will be entered by an investigator into an excel database in an anonymized format, locked with a password and kept on a KCH computer. PII will be kept on a different Excel file on a different KCH computer, also locked with a different password than the other file. KCH computers are located in the same office which is locked and accessible to the investigators only.

King’s College Hospital will keep identifiable information about participants for 12 months after the study has finished.

During study conduct, data will be reviewed to ensure that the protocol and Good Clinical Practices are being followed. Source document may be reviewed to confirm that data recorded on the CTF is accurate. The site may be subject to review by the Independent Ethics Committee and/or to inspection by appropriate regulatory authorities. The investigator and relevant personnel will ensure that they will be available during monitoring and possible audits and inspections.

# PEER AND REGULATORY REVIEW

The study has been peer reviewed in accordance with the requirements outlined by KCH R&I.

The study was deemed to require regulatory approval from the following bodies (list). Each approval will be obtained before the study commences. The Confidentiality Advisory Group (CAG) approval is not necessary for this study as the researchers will not intend to access confidential information without patient consent.

* HRA
* NeuroRag
* REC

# ASSESMENT AND MANAGEMENT OF RISK

The primary potential risk in this study is associated with the medical procedure (modified Valsalva Test).

This test is performed by exhalation into the spigot of the rubber connecting tube of an aneroid sphygmomanometer to a pressure of 60 mm Hg and maintaining this for 10 seconds. This approximates to a maximal voluntary Valsalva manoeuvre using such a device. Normal subjects experience mild light headedness and ‘head rush’ with this procedure but do not experience headache. However, some cough headache patients reported severe headache that closely resembled their primary symptom, resolving within a few minutes of stopping the forced exhalation (9).

As this procedure is commonly used in a clinical setting with a strong safety record, the investigators believe that the risks are almost none considering published data (9).

# RECORDING AND REPORTING OF EVENTS AND INCIDENTS

## 14.1 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. |

## Assessments of Adverse Events

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

* + 1. **14.2.1 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 |

* + 1. **14.2.2 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.

If a differentiated causality assessment which includes other factors in the study is deemed appropriate, please add/amend the following wording to specify:

It is of particular importance in this study to capture events related to the product application procedure (lumbar puncture). The assessment of relationship of an adverse event to this/these additional safety issue(s) will also be carried out as part of the study.

The differentiated causality assessments will be captured in the study specific CRF/AE Log and/or SAE form (amend as required).

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. |

* + 1. **14.2.3 Expectedness**

|  |  |
| --- | --- |
| Category | Definition |
| *Expected* | An adverse event which is consistent with the information about the procedure listed in the patient information sheet **or clearly defined in this protocol.** |
| *Unexpected* | An adverse event which is not consistent with the information about the procedure listed in the patient information sheet **or clearly defined in this protocol.** |

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

## Recording adverse events

All Adverse events will be recorded in the CRF following consent until the participant completes the study. All adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate.

## 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 (the sponsors AE log is used to collate SAEs and AEs so that the CI can review all in one place for trend analysis. If this data will be collated on a database throughout the study, from which a line listing of the SAEs can be extracted for review, an AE log will not be required).

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

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

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

**Is the event specified as an adverse event which does not require immediate reporting as an SAE?**

See section 16.5.

**Was the event an Other Notifiable event?**

See section 16.5 for notifiable events which should also be reported as serious

**Submit SAE form to Sponsor within 5 working days**

Record in medical records, CRF (and AE Log if required)

**Complete an SAE report form**

No

Yes

Record in medical records,

And CRF in accordance with the protocol

Yes

Yes

Record in medical records and CRF (if applicable)

No

No

**Was the event Serious?**

**AE occurs**

**Assign Severity Grade**

### 14.5 Serious Adverse Events that do not require reporting

All SAEs are to be reported.

## Reporting Urgent Safety Measures

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

## Protocol deviations and notification of protocol violations

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

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

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

(b) the scientific value of the study.

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

## 16.8 Reporting incidents involving a medical device(s) (if applicable)

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.

Additional sites are to report to central study coordinator who will submit a report to the manufacturer).

Incidents should be reported as soon as possible (usually within 24 hours).

Local trust reporting procedures may also need to be followed. It is the responsibility of the PI and study site team to ensure they are aware of any specific local requirements for reporting device incidents.

## 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:

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

Additional sites must adhere to the local policy and procedures concerning incidents and near misses.

# MONITORING AND AUDITING

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

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

# TRAINING

The Chief 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. Medical licences, GCP certificates and CV records will be kept in the site files with renewal dates monitored by the Chief Investigator. Only staff qualified an experienced in performing venepuncture and lumbar puncture procedures, as determined by the Chief Investigator, will be authorised to perform these procedures.

# INTELLECTUAL PROPERTY

N/A

# INDEMNITY ARRANGEMENTS

KCH 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.

# ARCHIVING

Archiving will take place locally at each site with essential documentation held for twelve months or the required local archiving time, whichever is longer. Any data held electronically will be transferred to CD-ROM and archived with the paper files.

# PUBLICATION AND DISSEMINATION POLICY

The results of this study will be published in acclaimed international journals, relevant to the field of study.

# APPENDICES

**Appendix 1:** **PROTOCOL VERSIONS**

|  |  |  |  |
| --- | --- | --- | --- |
| **Version Stage** | **Versions No** | **Version Date** | **Appendix No detail the reason(s) for the protocol update** |
| Current | **2.2** | **28th January 2019** | Final version |
| Current | 2.1 | 22nd January 2019 | Modified version |
| Previous | 2.0 | 15th January 2019 | Modified version |
| Previous | 1.2 | 18th December 2018 | Modified version |
| Previous | 1.1 | 8th November 2018 | Initial version |
| Previous | 1.0 | 12th July 2018 | Draft version |

# REFERENCES

1. Symonds C. Cough headache. Brain.1956; 79:557–568.

2. Ozge C, Atis S, Ozge A, Nass Duce M, Saracoglu M, Saritas E (2005) Cough headache: frequency, characteristics and the relationship with the characteristics of cough. Eur J Pain. 2005; 9: 383–388

3. Pascual J, Iglesias F, Oterino A, Vázquez-Barquero A, Berciano J. Cough, exertional, and sexual headaches. An analysis of 72 benign and symptomatic cases. Neurology. 1996;46: 1520-1524.

4. Pascual J, González-Mandly A, Martín R, Oterino A. Headaches precipitated by cough, prolonged exercise or sexual activity: A prospective etiological and clinical study. J Headache Pain. 2008; 9: 259-266.

5. Álvarez R, Ramón C, Pascual J. Clues in the Differential Diagnosis of Primary vs Secondary Cough, Exercise, and Sexual Headaches. Headache. 2014; 54:1560-1562.

6. Chen PK, Fuh JL, Wang SJ. Cough headache: a study of 83 consecutive patients. Cephalalgia. 2013; 29:1079–1085

7. Headache Classification Committee of the International Headache Society (IHS). *The International Classification of Headache Disorders*, 3rd edition. *Cephalalgia* 2018; 38:1‐211.

8. Gupta VK. Ocular compression maneuvre aborts benign cough induced headache. Headache. 2005; 45:612–614.

9. Lane RJ, Davies PT: Modified Valsalva test differentiates primary from secondary cough headache. J Headache Pain 2013, 14:31–40.

10. Cordenier A, De Hertogh W, De Keyser J, Versijpt J. Headache associeted with cough: a review. J Headache Pain. 2013; 14: 42.

11. Chen Y-Y, Linrng J-F, Fuh J-L, et al: Primary cough headache is associated with posterior fossa crowdedness: a morphometric MRI study. Cephalalgia. 2004, 24:694–699.