FULL/LONG TITLE OF THE STUDY	**Cognitive, behavioural and blood biomarker assessment after carbon monoxide (CO) exposure**
SHORT STUDY TITLE / ACRONYM	**Cognitive and blood biomarker assessment after CO Exposure**
PROTOCOL VERSION NUMBER AND DATE	**Version number: 1.0** **14th December 2019**
IRAS Number:	**277742**
JRES Reference Number	**2019.0375**
CHIEF INVESTIGATOR	**Peter Jenkins**
This protocol has regard for the HRA guidance and order of content	

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 Sponsor's 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 the Study Sponsor:

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

.....

Name (please print):

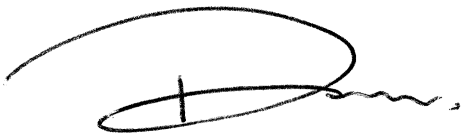
.....

Position:

.....

Chief Investigator:

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

Signature: 

Name: Peter Jenkins

KEY STUDY CONTACTS	
Chief Investigator	Dr Peter Jenkins Neurology Department Atkinson Morley Wing, St George's Hopsital Blackshaw Road London SW17 0QT Tel: 02087254631 email: peter.jenkins1@nhs.net
Sponsor	St Georges University Hospitals NHS Foundation Trust **SPONSOR REPRESENTATIVE:** Name: Subhir Bedi, Head of Research Governance and Delivery **SPONSOR CONTACT:** Name: Joe Montebello Address: St George's Joint Research Enterprise Service, Hunter Wing, Ground Floor, St George's, University of London and St George's University Hospitals NHS Foundation Trust, Cranmer Terrace SW17 ORE Email: researchgovernance@sgul.ac.uk Phone: 020 82666866
Funder(s)	This study is funded by the Gas Safety Trust

STUDY SUMMARY	
Study Title	**Cognitive, behavioural and blood biomarker assessment after carbon monoxide (CO) exposure**
Internal ref. no. (or short title)	**Cognitive and blood biomarker assessment after CO Exposure**
Study Design	Cohort observational
Study Participants	Individuals with proven raised levels of carboxyhaemoglobin (COHb) (>1.6% in non-smokers and >6.3% in smokers) or proven exposure to CO Exclusion criteria: • age <18 years • other significant neurological condition • smoke inhalation
Planned Size of Sample (if applicable)	50
Follow up duration (if applicable)	NA
Planned Study Period	18 months
Research Question/Aim(s)	(1) To determine whether blood biomarkers sensitive to neuronal injury are elevated in the sub-acute to chronic period following confirmed environmental, non-fire

	related exposure to CO. (2) Establish whether the prevalence of neurological, cognitive and behavioural deficits associated with CO exposure can be estimated; (3) Develop a sensitive and specific neurocognitive testing battery for CO poisoning (4) Characterize the neurological, cognitive and behavioural impairments following a confirmed CO poisoning event

FUNDING AND SUPPORT	
FUNDER(S)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
Gas Safety Trust 4 More London Riverside London SE1 2AU Tel: 0207 706 5100 Email: info@energynetworks.org	Providing financial support for the study. Also providing support regarding dissemination of findings

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Trial Steering Group:

Membership will consist of personnel involved in daily operational issues in the management of the study and will act upon advice/recommendations received by the sponsor.

Trial Steering Group	
Chair	Dr Peter Jenkins, Neurology Consultant, Atkinson Morley Wing St George's University Hospitals NHS Foundation Trust, London SW17 0QT
Member	Professor Richard Atkinson Population Health Research Institute St George's, University of London, Cranmer Terrace, London SW17 0RE **Statistical support**
Member	Ms Clara Bannister, Neurosciences Research Coordinator St George's University Hospitals NHS Foundation Trust, London SW17 0QT **Study support including administration, assessments and blood taking**

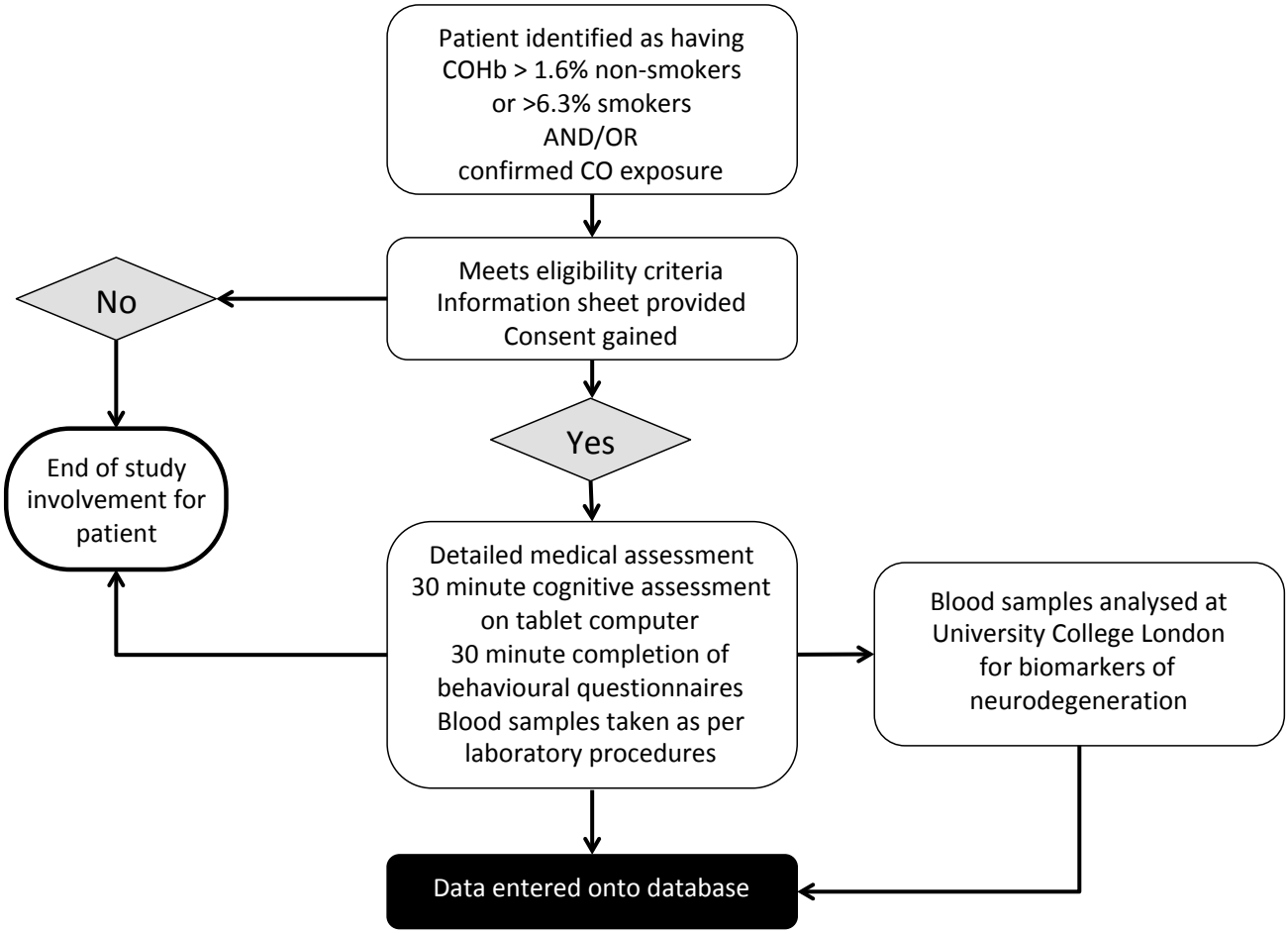
PROTOCOL CONTRIBUTORS

The protocol was conceived and designed by Dr Peter Jenkins.

The All-Party Parliamentary Carbon Monoxide Group (a government body with the aims of tackling carbon monoxide poisoning, improving government policy on carbon monoxide safety and to raise public awareness of this issue) supported the study proposal and will aid the dissemination of results.

The Gas Safety Trust, the study funder, will aid dissemination of results but will not control study design, analysis, interpretation or manuscript writing.

STUDY Schematic



ABBREVIATIONS	
AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CO	Carbon Monoxide
CRF	Case Report Form
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
ICF	Informed Consent Form
NHS	National Health Service
NIHR	National Institute for Health Research
PI	Principal Investigator
REC	Research Ethics Committee
SAE	Serious Adverse Event
SGUL	St Georges, University of London
SGHFT	St Georges, University Hospitals NHS Foundation Trust
JRES	(St Georges) Joint Research and Enterprise Services

Cognitive and blood biomarker assessment after CO Exposure

STUDY PROTOCOL

Cognitive, behavioural and blood biomarker assessment after carbon monoxide (CO) exposure

1 BACKGROUND

Carbon monoxide is estimated to cause around 30 deaths[1], 200 admissions[2] and 4000 presentations to Emergency Departments (EDs) each year in the UK[3]. In the longer term, CO poisoning is recognised to cause persistent neurological problems (including impairments of thinking and behavioural changes), which can develop days to weeks after the initial exposure[4]. However, the incidence of these long-term sequelae is unknown[4]. In addition, there is evidence of long-lasting inflammatory changes in the brain and on-going brain cell injury, although how long this persists is also unknown[5]. One long-term follow up study 33 years after a large CO poisoning mining accident showed over 70% of those affected had evidence of cerebral atrophy (loss of brain volume)[6], which may suggest evidence of persistent brain cell injury.

Initial assessments of CO exposure can be unreliable if blood tests are not carried out within a relatively short period after the exposure[7] and other biomarkers (such as imaging[8]) are insensitive to detecting previous CO exposure. Furthermore, chronic low-level exposure to CO poisoning can cause significant neurological deficits even with relatively low CO blood levels[9].

Certain proteins that are found in brain cells can be detected in the blood of individuals following brain injury and brain cell death. These proteins have been found to be raised in the acute period after minor head injury[10], persistently raised in patients with a traumatic brain injury and evidence of on going neurodegeneration (i.e. on going brain cell death)[11] and in patients with various types of dementia[12].

We will assess the presence of these proteins in the blood of 50 patients with proven CO exposure in the sub-acute to chronic timescale (2 weeks to 2 years). This has not been done before and will allow assessment of the presence of on going brain injury in these patients. We will also assess cognitive (e.g. memory, attention and speed of thinking) and behavioural impairments in these patients to help characterise the common impairments suffered following CO exposure.

2 RATIONALE

2.1 Primary aim:

To determine whether blood biomarkers sensitive to neuronal injury are elevated in the sub-acute to chronic period following confirmed environmental, non-fire related exposure to CO.

2.2 Secondary aims:

- Establish whether the prevalence of neurological, cognitive and behavioural deficits associated with CO exposure can be estimated;
- Develop a sensitive and specific neurocognitive testing battery for CO poisoning
- Characterize the neurological, cognitive and behavioural impairments following a confirmed CO poisoning event

Cognitive and blood biomarker assessment after CO Exposure

Current methods for detecting neurological injury due to CO exposure are unreliable yet the importance of neurocognitive changes found in people who have suffered from CO exposure are well depicted in case study reports[13]. There is therefore a need to identify those patients with chronic neurological problems due to CO exposure.

Measurements of certain proteins in the blood (in particular neurofilament light (NFL)) have become increasingly sensitive over recent years to detect the presence of injury to brain cells. These proteins are present inside brain cells and if the brain cells are injured they are released into the blood. These proteins have been found to be raised in the acute period after minor head injury[10], persistently raised in patients with a traumatic brain injury and evidence of on going neurodegeneration[11] and in patients with dementia[12]. Determining whether these blood biomarkers are raised following CO exposure is therefore important in order to be able to establish whether there is evidence of persistent brain injury in the sub-acute to chronic time frame after CO exposure.

Currently, it can be hard to determine whether an individual has had CO exposure as COHb levels rapidly normalise and if not taken quickly following exposure will be normal. It is therefore important to determine whether there are key cognitive and/or behavioural impairments following CO exposure and how best to measure them.

3 THEORETICAL FRAMEWORK

We will assess patients with proven exposure to CO in the sub-acute to chronic time period (2 weeks to 2 years after exposure). This will allow assessment of the use of blood biomarkers in this cohort that could be used in future patients with suspected but not proven CO exposure.

We will also use a cognitive testing battery that is validated in traumatic brain injury patients and will determine whether it is useful at characterising a profile of cognitive impairment following CO exposure.

4 RESEARCH QUESTION/AIM(S)

4.1 Primary aim:

To determine whether blood biomarkers sensitive to neuronal injury are elevated in the sub-acute to chronic period following confirmed environmental, non-fire related exposure to CO.

4.2 Secondary aims:

- Establish whether the prevalence of neurological, cognitive and behavioural deficits associated with CO exposure can be estimated;
- Develop a sensitive and specific neurocognitive testing battery for CO poisoning

- Characterize the neurological, cognitive and behavioural impairments following a confirmed CO poisoning event

4.3 Outcomes:

Blood biomarker levels in patients with proven CO exposure.

Cognitive and behavioural profiles of patients with proven CO exposure

5 STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYIS

The study will take place at St George's Hospital.

5.1 Methods:

A prospective observational study of patients with confirmed CO exposure. All patients will be fully assessed with a full neurological assessment and examination, a detailed battery of cognitive tests, behavioural questionnaires and blood biomarkers sensitive to persistent neuronal (brain) injury:

- The study will use Cogniclinic, a set of brief computerised cognitive tests that can be undertaken on a tablet computer which have been validated in other forms of acquired brain injuries including traumatic brain injury. This form of cognitive assessment benefits from the fact that it is easy to use and can be used in any setting. The App is free and was developed by researchers at Imperial College, London (https://quicktech.imperialinnovations.co.uk/i/software_apps/cognitron.html)

- Patients will also complete a full set of validated behavioural questionnaires that assess quality of life, depressive symptoms, anxiety levels, post-traumatic stress symptoms, fatigue, apathy, return to work and a newly developed questionnaire that will aim to identify the presence of common post-CO exposure symptoms.

- Two 4ml samples will be taken which will be sent to the UK Dementia Research Institute at UCL (Henrick Zetterberg's Group) to test for neurological blood biomarkers. Research blood sample bottles will be labelled with a unique study identifier and processed according to study laboratory procedures. Blood samples will be sent to measure levels of protein biomarkers sensitive to neuronal injury. Neurofilament light (NfL) is a sensitive blood biomarker of persistent brain injury and neuronal loss. Increased levels are observed in a variety of neurodegenerative diseases, including Alzheimer's disease and motor neuron disease. Levels also remain elevated in the chronic phase after a traumatic brain injury in some individuals and relate to evidence of progressive brain atrophy (shrinkage). This maybe relevant after CO exposure as some patients have progressive symptoms and it is a possible risk factor for the development of dementia. Blood biomarkers will include NfL, tau and glial fibrillary acidic protein.

Once enrolled, participants will be given a unique study identifier that will be used for all data collection, tests and blood samples. All data will be stored on a password-protected database on the Hospital's servers accessible to just members of the research team. Statistical analysis will be conducted using SPSS and R. Data analysis will take place at St George's hospital and with members of the research team based at St George's University of London. The unique study identifier will be linked to the individuals' personal data on a separate password-protected database held on the Hopsital's servers.

Cognitive tests and questionnaires will be compared to those from large normative control databases to identify differences between the study group (participants exposed to CO) and healthy controls. Blood tests will also be compared to a database of healthy controls to identify changes in these biomarkers after CO exposure.

The relationship between the blood biomarkers and cognitive tests/behavioural questionnaires will also be analysed to see whether there is a correlation between cognitive/behavioural impairments and evidence of brain cell injury as identified by the blood biomarkers.

Data collected from the cognitive tests and the questionnaires will be transcribed onto the main study database as soon after completion as possible. All results will be ascribed to the participants study identifier and no personal identifiable data will be included in the results database. Paper copies of the questionnaires will be kept with the participant files in a locked filing cabinet in a locked room. The blood samples will be sent as a batch with only the unique study identifier at the end of the study for analysis. No personal identifiable data will be sent with the blood samples. The results will be returned electronically via a password-protected encrypted database and transcribed to the main study database.

The data will be archived according to the Sponsor's standard operative procedure.

6 STUDY SETTING

The study will take place at St George's Hospital and is a single centre study.

Patients will have confirmed CO exposure as detailed below and will be assessed in the sub-acute to chronic timeframe (2 weeks to 2 years post exposure). Participants will be considered eligible for enrolment into this study if they fulfil all of the inclusion criteria and none of the exclusion criteria as defined below.

Participants will be identified via a National NHS clinic at St George's Hospital, London that assesses and treats patients with previous CO exposure.

7 SAMPLE AND RECRUITMENT

7.1 Eligibility Criteria

50 individuals with confirmed evidence of CO exposure will be recruited. This will allow assessment of common sequelae after CO exposure.

7.1.1 Inclusion criteria:

- Individuals identified as having confirmed exposure to CO between 2 weeks to 2 years at time of assessment. CO exposure determined by either;
    - documented COHb levels above 1.6% in non-smokers and above 6.3% in smokers.
    - or, individuals with evidence of being exposed to raised levels of CO and symptoms

7.1.2 Exclusion criteria:

- age <18 years
- actual or suspected smoke inhalation
- significant neurological or psychiatric illness prior to CO exposure
- inability to provide consent

7.2 Sampling

7.2.1 Size of sample

50 participants will be recruited.

The average value for serum neurofilament light (NFL) in a large sample of healthy controls was 22.9pg/ml (IQR 16.8-31.4) (Disanto G, Barro C, Benkert P, et al. Serum neurofilament light: a biomarker of neuronal damage in multiple sclerosis. Annals of neurology. 2017 Jun;81(6):857-70).
Using a sample of size of 50 allows an effect size of 0.46 on serum NFL levels to be detected with power 0.9 and type 1 error rate of 5%.
This sample size allows a relatively small change in serum NFL levels to be detected but as we do not know whether all CO exposed patients will have raised levels and we will have a range of levels of exposure, this sample size will allow us to explore these issues.

7.2.2 Sampling technique

A convenience sampling technique will be employed with participants identified via a National NHS clinic at St George's Hospital, London that assesses and treats patients with previous CO exposure. All participants will have confirmed exposure to CO and individuals with only suspected exposure will not be included. If eligible for participation, patients will be provided with an information leaflet and asked if they would like to participate. Any individual with confirmed CO exposure can be referred into this clinic nationally. It is also linked to an on going study, the EDCO study (IRAS 248936), which is screening individuals for carbon monoxide exposure in emergency departments. Individuals identified as having been exposed to CO from this study will be offered a follow up in this clinic. This sampling technique has been used to optimise recruitment given the fact CO exposure is relatively rare.

7.2 Recruitment

Patient recruitment will only commence once evidence of the following approval / essential documents are in place:

1. REC approval
2. Final sponsorship permissions,

Participant Identification

Potential participants will be reviewed in a specialist Neurology outpatient clinic designed to assess and manage patients exposed to CO with neurological problems.

This clinic is linked to a current research study (the EDCO study, a study screening for carbon monoxide exposure in emergency departments). Patients identified as having been exposed to CO will be routinely referred in to this clinic for clinical care. The PI for this study is the clinical lead for this outpatient clinic and will therefore have access to identifiable personal data in order to provide the clinical care and will be able to review the medical records in order to be able to determine suitability.

Any patient nationally with confirmed CO exposure can be referred to this clinic but recruitment to the study will only occur once patients are reviewed in the clinic and participants to the study will not be recruited via other channels. The clinic will be publicised so that other healthcare professionals are aware of it so that patients can be assessed and reviewed clinically.

7.2.1 Consent

The Principal Investigator (PI), or an appropriately trained member of the team will obtain informed consent. Eligible patients will be provided with a written patient information sheet describing the study and the study team will be available to answer any questions. The patient will be given adequate time to read the information and consider their participation in the study. Due to the perceived low risk, burden and minimally invasive nature of the study, consent will be sought during the same routine clinic appointment in which patients are approached about the study by the clinical team. If they wish to take part they will then go through the written consent process.

The patient will be informed that their medical records are subject to review by representatives of the sponsor as necessary and that data will be collected and processed in accordance with the Data Protection Act 2018. The patient will be told that participation in the study is voluntary and that they are free to withdraw from the study at any time and without prejudice. If patients are willing to provide a reason for their withdrawal, this information will be recorded. Each patient will be advised that data collected may be published or presented at scientific meetings and may also be subject to audit procedures from Regulatory Authorities. All such personally identifiable data will be pseudo-anonymised to maintain patient confidentiality.

A copy of the signed Informed Consent Form (ICF) along with a copy of the most recent approved Patient Information Sheet (PIS) will be given to the study participant. The original signed & dated consent form will be placed in the ISF and a copy retained in the medical notes.

If new information results in significant changes to the risk–benefit assessment, the consent form will be reviewed and updated if necessary. All participants, including those already being treated, will be informed of the new information, given a copy of the revised consent form and asked to re-consent if they choose to continue in the study.

7.2.2 **Data collection tool**

Paper Case Report Forms (CRFs) will be used. All data will be entered legibly in black ink with a ball-point pen. If the investigator makes an error, it will be crossed through with a single line in such a way to ensure that the original entry can still be read. The correct entry will then be clearly inserted. The amendment will be initialled and dated by the person making the correction immediately. Overwriting or use of correction fluid will not be permitted.

It is the investigator's responsibility to ensure the accuracy of all data entered and recorded in the CRFs. The *delegation of responsibilities log* will identify all study personnel responsible for data collection, entry, handling and managing the database.

Patients will undergo a full medical history and examination. Data including COHb levels at time of exposure, medical and drug history will initially be entered into the medical notes as part of routine clinical care and if the participant wishes to take part in the study the relevant data will be transcribed onto the paper CRF.

Behavioural questionnaires and cognitive assessment results will be entered into a password-protected spreadsheet/database on the NHS computing network.

7.2.3 Biological Sample Handling

Sample collection

Two samples of 4-5ml each to be collected from each participant:

- Serum (gel tube). One 10 or 7mL tube
- Plasma(EDTA-K2 tube, purple cap). One 10 or 7mL tube

Processing at St George's lab

Tubs will be mixed by turning up and down 8-10 times. The serum sample will be allowed to coagulate for >30 min.

Serum:

After coagulation, it will be centrifuged at 2500 x g for 20 minutes with temperature set at +4°C.

Plasma:

It will be centrifuged at 2500 x g for 20 minutes with temperature set at +4°C.

Aliquotation and storage

0.5-1.0 mL aliquots of the samples will be pipetted into cryotubes.

All tubes will be labelled (patient unique studyID, date etc.) and frozen immediately at -80^{o}C.

Samples will be stored at St. George's Hospital until all samples have been collected. Samples will then be sent in bulk by specialist courier to the UK Dementia Research Institute at UCL (Henrick Zetterberg's Group) to test for neurological blood biomarkers. Upon completion of sample analysis, remaining sample material will be disposed in accordance with the Human Tissue Authority's Code of Practice.

7.3 Confidentiality

All data will be handled in accordance with the Data Protection Act 2018. Only delegated members of the research team, who form part of the direct clinical care team will have access to patient identifiable data.

Once written informed consent has been obtained for study participation, the patient will be allocated a unique study identifier (consisting of a site number and sequential participant number), which will be utilised to code all depersonalised data. The patient's unique study number (ID) only, will be used for identification.

As no personal identifiable data is being collected, there will be no personal identifiable data included in the results.

7.4 Archiving arrangements

The essential study documents along with the study database will be archived in accordance with the sponsor SOPs. The agreed archiving period for this study will be 10 years.

7.5 Direct access to source data

The investigator(s)/institution(s) will permit sponsor / study-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Study participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

8 ETHICAL AND REGULATORY CONSIDERATIONS

The study will be conducted in compliance with the protocol as agreed by the Sponsor and which was given favourable opinion by the Research Ethics Committee (REC) and Health Research Authority (HRA).

The Chief Investigator will be provided (via the Sponsor) with file indexes. The CI will be responsible for the maintenance of the TMF.

Within 90 days after the end of the study, the CI and Sponsor will ensure that the REC is notified that the study has finished by completing the Sponsor's 'End of study declaration'.

The CI will supply an End of Study report of the clinical study to the REC within one year after the end of the study. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

8.1 Assessment and management of risk

Participants will be identified and recruited via a specialist neurology clinic treating patients with CO exposure. If the research team identify concerns regarding potential harm to the patient, e.g. concerns regarding the participant's mental health, then these will be discussed with the research team clinician (Dr Peter Jenkins) and appropriate action taken. A similar management plan will be instituted if the participant discloses information about intention to harm others to members of the research team.

8.2 Research Ethics Committee (REC) and other Regulatory review & reports

Before the start of the study, a favourable opinion will be sought from an appropriate REC for the study protocol, informed consent forms and other relevant documents e.g. advertisements.

- Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site.
- It is the Chief Investigator's responsibility to produce the annual reports and submit the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.
- The Chief Investigator will notify the REC of the end of the study within one year after the end of the study.
- If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

Regulatory Review & Compliance

Before any site can enrol patients into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance.

Amendments

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

8.3 Peer review

The study was peer reviewed via a competitive funding application by the funder, the Gas Safety Trust. Award of the funding entailed expert review and panel interview.

8.4 Patient & Public Involvement

The grant proposal has been discussed and endorsed by the All-Party Parliamentary Carbon Monoxide Group which encompasses clinicians, policy makers and patient representatives/advocates. This group meets regularly and will allow feedback on the study and aid the dissemination of the findings.

In addition, the funder of the study, the Gas Safety Trust, will aid dissemination of the results.

8.5 Protocol compliance

Protocol deviations, non-compliances, or breaches are departures from the approved protocol.

All protocol deviations must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

8.6 Data protection and patient confidentiality

All data will be handled in accordance with the Data Protection Act 2018 (UK implementation of the EU General Data Protection Regulation (GDPR)).

Consent forms will be the only data collected during the study that will contain patient identifiable data. Once completed these will be stored in a locked filing cabinet in a locked office only accessible to delegated members of the research team.

Any Case Report Forms (CRFs) will not bear the participant's name or other directly identifiable data. The participant's trial Identification Number (ID) only, will be used for identification. The Subject ID log can be used to cross reference participant's identifiable information. The Subject ID log will be password-protected and stored on the St George's Hospital servers. It will only be accessible to delegated members of the research team.

Clinical data including cognitive testing and behavioural questionnaires will be uploaded to a password-protected database with the participant's unique identifier. Clinical data will also include details of CO exposure (i.e. COHb levels), other medical history and medication history. Basic participant demographic data (e.g. gender, age, medical history) will also be recorded. Blood samples will be sent to the laboratory at UCL with no patient identifiable data and results will be sent back via secure email, again with no patient identifiable data. These results will be uploaded to the database. The database will be held on the St George's Hospital IT infrastructure and will only be accessible to delegated members of the research team. The data will be kept for 10 years after the study and then deleted.

Data will be analysed at both St George's Hospital and also at St George's University of London. Data will be transferred electronically via encrypted password-protected files to the University with no patient identifiable data (just the unique study identifiers).

8.7 Indemnity

St Georges University Hospitals NHS Foundation Trust is party to NHS Litigation Authority (NHSLA) / NHS Resolution. As an NHS body it is liable for clinical negligence and other negligent harm to individuals covered by their duty of care. NHS Institutions employing researchers are liable for negligent harm caused by the design of studies they initiate.

8.8 Access to the final study dataset

Members of the research team will have access to the full dataset. Patients will be consented for possible secondary analysis through possible future research projects.

9 DISSEMINATION POLICY

9.1 Dissemination policy

Publication: “Any activity that discloses, outside of the circle of trial investigators, any final or interim data or results of the Trial, or any details of the Trial methodology that have not been made public by the Sponsor including, for example, presentations at symposia, national or regional professional meetings, publications in journals, theses or dissertations.”

All scientific contributors to the Trial have a responsibility to ensure that results of scientific interest arising from Trial are appropriately published and disseminated. The Sponsor has a firm commitment to publish the results of the Trial in a transparent and unbiased manner without consideration for commercial objectives.

To maximise the impact and scientific validity of the Trial, data shall be consolidated over the duration of the trial, reviewed internally among all investigators and not be submitted for publication prematurely. Lead in any publications arising from the Trial shall lie with the Sponsor in the first instance.

Before the official completion of the Trial,

All publications during this period are subject to permission by the Sponsor. If an investigator wishes to publish a sub-set of data without permission by the Sponsor during this period, the Study Management Group shall have the final say.

Exempt from this requirement are student theses that can be submitted for confidential evaluation but are subject to embargo for a period not shorter than the anticipated remaining duration of the trial.

Up to 180 days after the official completion of the Trial

During this period the Chief Investigator shall liaise with all investigators and strive to consolidate data and results and submit a manuscript for peer-review with a view to publication in a reputable academic journal or similar outlet as the Main Publication.

- The Chief Investigator shall be senior and corresponding author of the Main Publication.
- Insofar as compatible with the policies of the publication outlet and good academic practice, the other Investigators shall be listed in alphabetic order.
- Providers of analytical or technical services shall be acknowledged, but will only be listed as co-authors if their services were provided in a non-routine manner as part of a scientific collaboration.

- Members of the Study Management Group shall only be acknowledged as co-authors if they contributed in other capacities as well.
- If there are disagreements about the substance, content, style, conclusions, or author list of the Main Publication, the Chief Investigator shall ask the Study Management Group to arbitrate.

Beyond 180 days after the official completion of the Trial

After the Main Publication or after 180 days from Trial end date any Investigator or group of investigators may prepare further publications. In order to ensure that the Sponsor will be able to make comments and suggestions where pertinent, material for public dissemination will be submitted to the Sponsor for review at least sixty (60) days prior to submission for publication, public dissemination, or review by a publication committee. Sponsor's reasonable comments shall be reflected. All publications related to the Trial shall credit the Chief and Co-Investigators as co-authors where this would be in accordance with normal academic practice and shall acknowledge the Sponsor and the Funders.

9.2 Archiving Arrangements

The trial essential TMF along with any central trial database will be archived in accordance with the sponsor SOP.

10 REFERENCES

1. Cross Government Group On Gas Safety And Carbon Monoxide (CO) Awareness. Annual Report. 2014-2015.

2. Reducing the risk of carbon monoxide poisoning over winter [press release]. 2012. Available from: http://webarchive.nationalarchives.gov.uk/20140714084352/http://www.hpa.org.uk/NewsCentre/NationalPressReleases/2012PressReleases/121119Reducingtheriskofcarbonmonoxidepoisoning/ - 1._, 19 November 2012 2012

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11. APPENDICIES

Appendix 1

Amendment Log				
Amendment No.	**Protocol version no.**	**Date issued**	**Author(s) of changes**	**Details of changes made**