Carbogen for Status Epilepticus in Children Trial

(CRESCENT)

Seizure control via pH manipulation: a phase II double blind RCT of inhaled carbogen as adjunctive treatment of paediatric convulsive status epilepticus

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Trial Sponsor:

The Newcastle upon Tyne Hospitals NHS Foundation Trust,
Freeman Rd, High Heaton, Newcastle upon Tyne NE7 7DN

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The Newcastle upon Tyne Hospitals NHS Foundation Trust

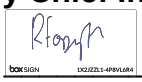
JOINTLY FUNDED BY
UKRI Medical Research Council
NIHR National Institute for Health Research

UNIVERSITY OF LIVERPOOL

PROTOCOL APPROVAL

I, the undersigned, hereby approve this clinical study protocol:

Authorised by Chief Investigator:

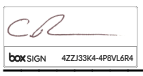
Signature:  **Date:** 13 Jul 2022

Dr Rob Forsyth

Senior Lecturer and Consultant Paediatric Neurologist, Newcastle University and Newcastle upon Tyne Hospitals NHS Foundation Trust

I, the undersigned, hereby approve this clinical study protocol:

Authorised on behalf of Sponsor:

Signature:  **Date:** 13 Jul 2022

Mr Chris Price (or colleague)

Deputy Regulatory Compliance Manager, The Newcastle upon Tyne Hospitals NHS Foundation Trust

I, the undersigned, hereby approve this clinical study protocol:

Authorised on behalf of the Lead Statistician:

Signature:  **Date:** 13 Jul 2022

Professor Carrol Gamble

Director of the Liverpool Clinical Trials Centre, University of Liverpool

General Information

This document describes the CRESCENT trial including detailed information about procedures and recruitment. The protocol should not be used as an aide-memoir or guide for the treatment of patients. Every care was taken in its drafting, but corrections or amendments may be necessary. Any amendments will be circulated to the investigators participating in the trial, but sites entering patients for the first time are advised to contact the coordinating centre (Liverpool Clinical Trials Centre, LCTC) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the Chief Investigator, Dr Rob Forsyth, via the LCTC.

This protocol defines the participant characteristics required for study entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements. Waivers to authorise non-compliance are not permitted.

Incidence of protocol non-compliance whether reported prospectively or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations. These are monitored and reported to trial oversight committees.

The template content structure is consistent with SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) and has regard for the Health Research Authority guidance. Regulatory and ethical compliance information is located in section 14.

The Liverpool Clinical Trials Centre (LCTC) brings together a wealth of expertise built on the experience of the Liverpool Trials Collaborative which has held full registration status with the UK Clinical Research Collaboration CTU network since its establishment in 2007 (www.ukcrc.org). The LCTC has a diverse trial portfolio underpinned by methodological rigour, a Good Clinical Practice (GCP) compliant data management system, and core standard operating procedures.

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The contact details for the trial oversight committee members and participating sites are detailed in documents supplementary to the protocol and stored in the Trial Master File.

1 Table of Contents

2 Glossary

APLS	Advanced Paediatric Life Support (resuscitation guidelines)
APR	Annual Progress Reports
ARCON	Accelerated Radiotherapy, Carbogen, and Nicotinamide (radiotherapy treatment protocol)
BOC	British Oxygen Company (supplier of medical gases)
CBF	Cerebral Blood Flow
CI	Chief Investigator
CNS	Central Nervous System
CRF	Case Report Form
CSE	Convulsive Status Epilepticus (see below for lay definition)
CTIMP	Clinical Trials of an Investigational Medicinal Product
CTU	Clinical Trials Unit
DSUR	Developmental Safety Update Reports
EcLiPSE	Emergency treatment with Levetiracetam or Phenytoin in convulsive Status Epilepticus (previous successfully completed clinical trial)
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
ED	Emergency Department (= Accident and Emergency department)
FiCO2	Proportion of carbon dioxide in inspired gas
GABA	Gamma-amino butyric acid
GCP	Good Clinical Practice
GP	General Practitioner
HCP	Health Care Professional
HRA	Health Research Authority
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IDSMC	Independent Data and Safety Monitoring Committee
IMP	Investigational Medicinal Product
IPD	Individual Participant Data
ISF	Investigator Site File (part of the Trial Master File)
ISRCTN	International Standard Randomised Controlled Trials Number
ITT	intention-to-treat
IWRS	Interactive Web Response System
LCTC	Liverpool Clinical Trials Centre
MA	Marketing Authorisation
MedDRA	Medical Dictionary for Regulatory Activities
MGDS	Medical Gas Data Sheet

MHRA	Medicines and Health care products Regulatory Agency
MRS	Magnetic Resonance Spectroscopy
NHS	National Health Service
NIHR EME	National Institute for Health Research Efficacy and Mechanism Evaluation (EME) programme
NUTH	Newcastle upon Tyne Hospitals NHS Foundation Trust (Sponsor)
ONS	Office for National Statistics
paCO2	Partial pressure of carbon dioxide in arterial blood
PERUKI	Paediatric Emergency Research in the UK and Ireland
PI	Principal Investigator
PICU	Paediatric Intensive Care Unit
PISC	Patient Information Sheet and Consent form
PPI	Patient and Public Involvement
PSF	Pharmacy Site File
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RN	Research Nurse (Registered)
RSI	Rapid Sequence Induction (of general anaesthesia)
RSO	Research Support Office
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
USM	Urgent Safety Measure

Convulsive Status Epilepticus – lay definition

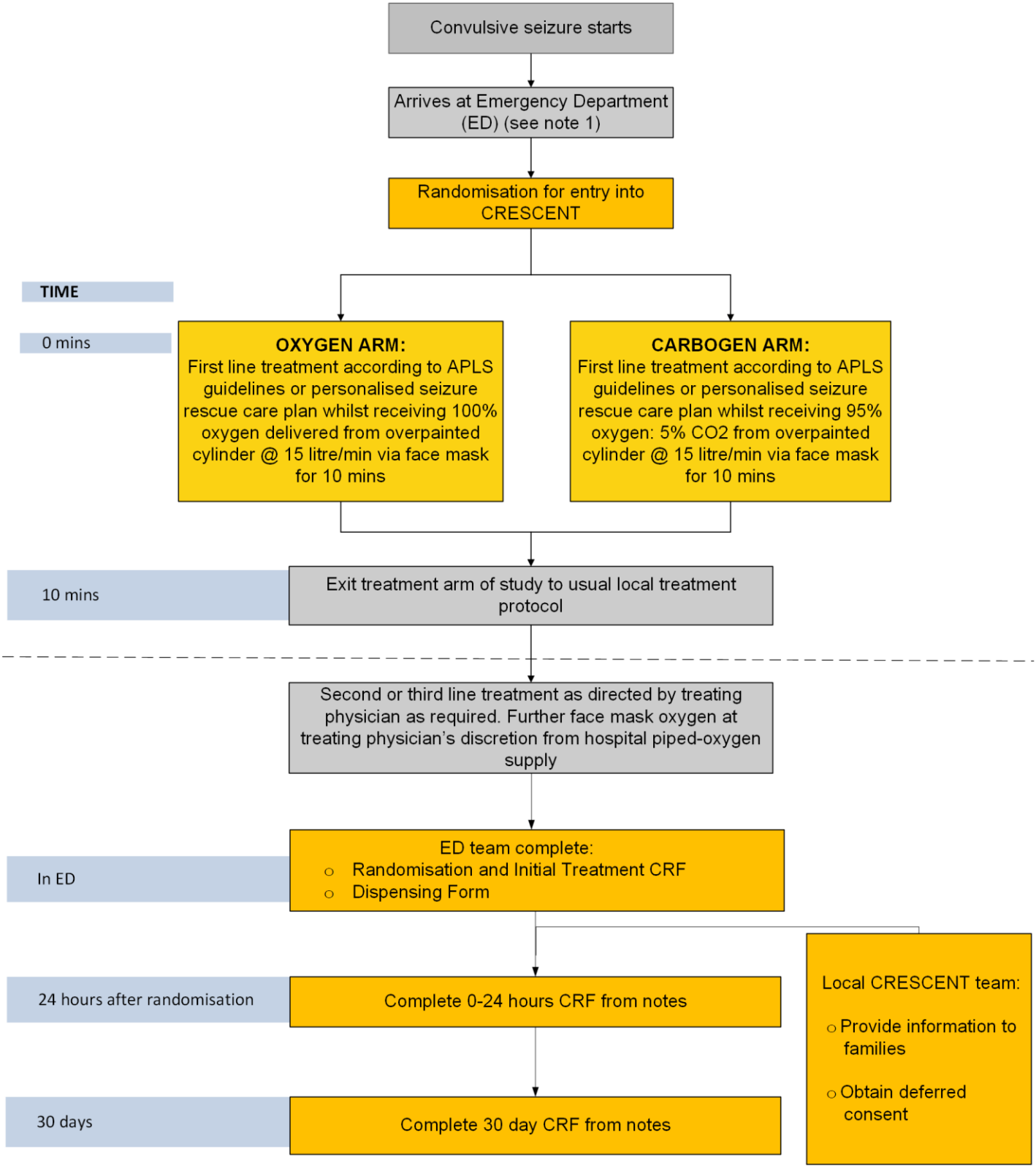
Most epileptic seizures and convulsions in children last less than three minutes and stop by themselves. However, the longer the seizure lasts the less likely it is to stop by itself. Long-lasting ongoing seizure activity is known as convulsive status epilepticus (CSE) and is a medical emergency because it can cause brain damage. To prevent CSE from happening children are given a medicine called a rescue or emergency medicine. Some families with children known to be prone to CSE are given emergency medicine to keep at home: they will typically be asked to give the medicine after five minutes of seizure activity. Other families will be asked to dial 999 after five minutes. Paramedic crews carry the emergency medicine.

3 Protocol Overview

Title	Seizure control via pH manipulation: a phase II double blind RCT of inhaled carbogen as adjunctive treatment of paediatric convulsive status epilepticus
Short Title	CaRbogEn for Status epilepticus in ChildrEN Trial (CRESCENT)
Phase	II
Target Population	Children in Convulsive Status Epilepticus (CSE): i.e. ongoing generalised or focal convulsive seizure activity requiring emergency treatment.
Sample size	424
Inclusion criteria	1. Presenting to Paediatric Emergency Department (ED) of a participating site 2. Exhibiting signs of Convulsive Status Epilepticus (CSE) (i.e. ongoing generalised tonic-clonic, generalised clonic or focal clonic convulsive seizure activity) requiring – in the view of the treating physician - emergency treatment either according to standard APLS guidelines or the child's personalised rescue care plan in order to try and terminate the presenting seizure
Exclusion criteria	1. Known to have been previously enrolled in CRESCENT 2. Infantile spasms (West Syndrome) 3. Non-epileptic seizure ("pseudo status epilepticus") 4. Tonic posturing due to suspected brain herniation 5. Has received phenytoin, levetiracetam, phenobarbital or valproate as part of the management of *this episode* of status epilepticus
Trial Sites and Distribution	Approximately 12 Paediatric EDs in NHS secondary and tertiary hospitals in the UK.
Patient Trial Duration	30 days
IMP / Intervention	**Carbogen (Intervention):** IMP: 5% carbogen alongside standard APLS medical management of CSE Form: Medical gas (5%CO_2: 95%O_2) Dose: 15 litres/min for ten minutes Route: Inhaled via non-rebreather face mask **Oxygen (Control):** IMP: e100% oxygen alongside standard APLS medical management of CSE Form: Medical gas (100%O_2) Dose: 15 litres/min for ten minutes Route: Inhaled via non-rebreather face mask
Objectives	To ascertain (i) the effectiveness of carbogen in enhancing response rates of conventional first-line treatments of CSE and (ii) its safety in this context.
Primary outcome	Success of first-line treatment of CSE (i.e. child did not need to receive second-line or rescue therapy as defined within the APLS guidelines or their personal treatment plan). Success of first line

	treatment is defined as not requiring intravenous phenytoin, phenobarbital, valproate, levetiracetam or RSI.
Secondary outcomes	• Seizure activity visible at 5 minutes, and 15 minutes post commencement of inhalation • Need for rapid sequence induction (RSI) with thiopentone or another agent (e.g. propofol) due to ongoing CSE • Need to be admitted to critical care or high dependency unit • Seizure recurrence within 24 hours • Serious adverse events and reactions • 30-day mortality
Exploratory analysis	Two prespecified, exploratory analyses will be conducted to examine whether there is a difference in response rates to carbogen in children who are: 1) more alkalotic on admission 2) deemed to have had a febrile CSE episode

3.1 Schematic of Trial Design



NOTE 1: First line emergency treatment may have commenced before arrival in ED

4 Roles and Responsibilities

Sponsor

The Sponsor is the Newcastle upon Tyne Hospitals NHS Foundation Trust (NUTH) and is legally responsible for the study. They will formally delegate specific duties to the Chief Investigator and Clinical Trials Unit via a Delegation of Duties Agreement.

Funder

This study is funded by the National Institute for Health Research (NIHR) National Institute for Health Research Efficacy and Mechanism Evaluation (EME) programme (NIHR EME Reference Number: NIHR129875). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Chief Investigator: Dr Rob Forsyth is the Chief Investigator (CI) for the trial and is responsible for overall design and conduct of the trial in collaboration with other members of the study team.

Principal Investigators: In each participating site a principal investigator (PI) will be identified to be responsible for identification, recruitment, data collection and completion of CRFs, along with follow up of study patients and adherence to study protocol at site. They will also be responsible for safety reporting and processing any applicable safety information.

Clinical Trials Unit: LCTC at the University of Liverpool in collaboration with the CI, will have overall management responsibility and will be responsible for trial management activities including (but not limited to) study planning, budget administration, Trial Master File management (limited to LCTC delegated duties), safety reporting, data management, randomisation, statistical analysis and participating site coordination.

British Oxygen Company (BOC): BOC will supply the IMP for CRESCENT. BOC are responsible for manufacturing the IMP, labelling the cylinders to ensure that the treatment allocation is blinded, providing QP certification**,** shipping the cylinders to sites and retrieving the used cylinders.

Oversight Committees

The CRESCENT trial is subject to oversight from the following committees:

Trial Management Group (TMG)

The Trial Management Group (TMG) is comprised of the Chief Investigator, co-applicants, Sponsor representative, Sponsor Pharmacy representative(s), PPI representative(s) and members of the LCTC. The TMG are responsible for monitoring all aspects of the progress and conduct of the trial and are responsible for the day-to-day running and management of the trial. The TMG will meet as defined in their terms of reference.

Trial Steering Committee (TSC)

The Trial Steering Committee consists of an independent chairperson (biostatistician/trialist), independent experts in the fields of paediatric emergency medicine and epilepsy, parent representatives, the CI and observers. The role of the TSC is to provide oversight for the trial and provide advice through its independent Chair. The TSC will consider recommendations of the

IDSMC. The TSC judgement on IDSMC recommendations for the continuation or amendment of the trial will be communicated to the trial Sponsor and funder. The TSC will meet throughout the trial (at least annually) in accordance with their terms of reference/charter.

The composition and membership of the TSC has been confirmed by NIHR EME as funder.

Independent Data and Safety Monitoring Committee (IDSMC)

The IDSMC consists of an independent chairperson plus two independent members, experts in the fields of paediatrics and paediatric epilepsy.

The composition and membership of the IDSMC has been confirmed by NIHR EME as funder.

The IDSMC will receive and review monitoring reports and interim analyses for the trial and provide recommendations on the conduct of the trial to the Trial Steering Committee in accordance with their terms of reference/charter.

5 INTRODUCTION

5.1 Background

Convulsive status epilepticus (CSE) is the most common neurological emergency in children affecting 20 per 100,000 children per year [1]. This equates to 4000 CSE events in England and Wales annually, of which half will be first-ever events in children who have never previously had a seizure. The first episode of CSE is a terrifying experience for parents, many of whom believe their child is dying [2]. The morbidity of CSE relates to cause and duration, and despite improved pre-hospital care mortality remains at 3% [1, 3]. Current treatment for CSE follows a standardised stepwise algorithm. Benzodiazepines (midazolam, lorazepam or diazepam) are given twice parenterally (typically buccally, intravenously or rectally respectively) with escalation to second-line treatments (traditionally phenytoin or phenobarbital, increasingly levetiracetam) if seizures have not stopped. If these fail, general anaesthesia is given via rapid sequence induction (RSI) and the child is admitted to an intensive care unit (ICU) [4]. Children with a history of multiple previous episodes of CSE will sometimes have a personalised seizure management plan drawing on this prior experience: such plans can use alternative first line medications including paraldehyde, but second line and subsequent management plans tend to converge on standard practice. Parenteral benzodiazepines become less effective with increasing CSE duration: suggested mechanisms include internalisation of GABA receptors [5] or the loss of GABA-A receptor conductance and chloride-extrusion function [6], hence the growing practice of supplying buccal midazolam for pre-hospital use. However, repeated benzodiazepine administration has a high risk of respiratory depression and contributes to ICU admission [7].

Lyttle *et al* have recently successfully completed EcLiPSe, a randomised controlled trial (RCT) comparing phenytoin and levetiracetam as second-line CSE treatments [8] in children who have failed to respond to a second dose of benzodiazepine. CRESCENT builds on the success of EcLiPSe, addressing the earlier, first stage of the CSE algorithm, aiming to improve the efficacy of first-line benzodiazepines, shorten duration of CSE and reduce the need for second line interventions, CSE-related morbidity, and hospital and ICU admission rates. CRESCENT draws on EcLiPSe for relevant aspects of its design.

Systematic Review

We have completed a systematic review of the literature comprising studies in humans (healthy volunteers or people with epilepsy) of induction of respiratory acidosis (by any means) with appropriate controls on any epilepsy-related outcome (seizure frequency or electroencephalographic (EEG) endpoints). Several established anticonvulsant medications are thought to act via carbonic anhydrase inhibition and the resulting increase in p_aCO_2 as either their main (e.g. acetazolamide [9]) or a component (e.g. topiramate, zonisamide [10]) of their mechanism of action. Although carbonic anhydrase inhibition will therefore also cause an acidosis the anticonvulsant effects of pharmacological carbonic anhydrase inhibitors was excluded from the literature review.

The primary literature search was performed in Medline on 12th November 2019 using Ovid Medline®, ePub ahead of print and in-process and other non-indexed citations 1946 to 11th November 2019. This Medline search was supplemented by searches of the Cochrane Database of Systematic Reviews and ClinicalTrials.gov. Full descriptions of the identified studies are available from the CI.

This systematic review has confirmed the existence of a small number of exploratory studies of F_iCO_2 manipulation in individuals with epilepsy although all are very under-powered. In attempting a synthesis, the evidence for the efficacy of F_iCO_2 manipulation is strongest in situations where baseline hyperventilation and hypocarbia is likely. This includes children with absence epilepsy [11], adults with coexisting hyperventilation states [12, 13] and potentially also children with febrile convulsions [14–17].

One unanswered question is whether the negative results e.g. in Mullen [18] reflect an inability of carbogen to affect a worthwhile incremental acidosis *additional* to that already due to the CSE itself: the result of sustained anaerobic contraction of peripheral muscles and/or respiratory acidosis due to seizure-related reductions in minute-volume. There are important reasons however to address this issue separately in children: as discussed above a high proportion particularly of younger children are convulsing in the context of a respiratory alkalosis due to fever (establishing whether a young child's seizure was related to fever is usually only retrospective) and the data on systemic pHs after CSE are adult: it is not known whether these values are achieved in children.

5.2 Rationale

Extensive pre-clinical and pilot data suggest that mild acidosis promotes seizure termination [19, 20]. Mild physiological acidosis can be achieved by replacing the oxygen typically delivered during management of CSE with carbogen, which still provides oxygen in large excess. We see carbogen as a simple potential enhancement of current best practice, with the possibility of improved response to first line treatments, leading to a reduction in repeated administration of benzodiazepines, and thus treatment-related morbidity. Carbogen will also provide modest respiratory stimulation. Rebreathing masks that recirculate exhaled air would be an alternative means of achieving respiratory acidosis, although the magnitude would be hard to control in the context of seizures affecting minute-volume. In addition, they would not deliver supplemental oxygen. Carbogen is cheap and easy to store. Carbogen is non-sedating and if shown to be safe and effective in this context could in principle be delivered in pre-hospital settings by families, teachers and paramedics.

Brain pH is 0.3 units more acidic than blood [21]: this compartmentation implies neurophysiological importance [22]. Several lines of evidence indicate a role for brain pH in seizure onset and termination. Respiratory alkalosis due to hyperventilation is a reliable trigger of seizures in Childhood Absence Epilepsy [11]. Fever-induced hyperventilation may contribute to the common paediatric phenomenon of febrile convulsion [14, 17]. Intentional induction of mild respiratory alkalosis increases seizure frequency and duration in the context of Electroconvulsive Therapy [23, 24]. Mixed metabolic and respiratory alkalosis also appears important in the genesis of seizures in neonatal hypoxic ischaemic encephalopathy (birth asphyxia) [25].

Precisely how pH shifts affect seizure propagation remains incompletely understood but a role for Acid-Sensing Ion Channel 1a has been suggested [26]. Intracellular acidification achieved by increasing the proportion of carbon dioxide inspired (F_iCO_2) terminates hypomagnesaemic [27] and bicuculline-induced [19] seizures in rodents and macaques. Seizure inhibition in a rodent audiogenic seizure model has been reported with F_iCO_2 of 5–15%. The anticonvulsant effects of acetazolamide (a carbonic anhydrase inhibitor) are at least in part due to the resulting increase in p_aCO_2 [9]. Carbonic anhydrase inhibition is also part of the mechanism of action of several established epilepsy medications including topiramate and zonisamide. A degree of seizure-related hypoventilation is seen even in focal seizures [28] and it is possible that respiratory and/or

metabolic acidosis may contribute to “spontaneous” seizure termination, although other processes of “metabolic exhaustion” are probably also important [29].

Although blood pH is strongly buffered, the brain is a separate compartment in relation to pH regulation, with a resting pH 0.3 pH units more acidic than blood and its own carbonic anhydrases [20] and thus blood buffering is actually not pertinent to CO2 effects on the brain. Carbogen inhalation results in a maintained increase in p_aCO_2 [30], even if buffering leads to secondary metabolic alkalosis and normalisation of the arterial pH. ^{31}P magnetic resonance spectroscopy (MRS) confirms that 5% carbogen inhalation by healthy human volunteers achieves a sustained fall in brain intracellular pH [21]. Acquisition of the MRS data in this study took 20 mins, confirming the sustained nature of the ΔpH and again the independence of intracerebral pH from any peripheral buffering. DC-EEG analysis in volunteers again indicates near instantaneous onset of carbogen effects on CNS neurophysiology that are again sustained despite rebuffering of blood pH [30, 31]. Carbogen-induced seizure termination in rodents is associated with cerebral extracellular ΔpH (measured continuously in real time by implanted electrode) of 0.05-0.1 units that persists for tens of minutes [14] despite presumed peripheral buffering (although peripheral pH was not examined in this study).

Clinical experience with carbogen

Carbogen is a commercially available medical gas mixture used in clinical radiotherapy (particularly “accelerated radiotherapy, carbogen, and nicotinamide” (ARCON) protocols [32]: the rationale for its use in this context being that tissue oxygenation is believed to enhance radio-sensitivity of tumours and carbogen achieves this more effectively than 100% oxygen inhalation as it causes additional vasodilation). This literature provides additional safety and tolerability data. Effects of carbogen inhalation are physiologically equivalent to rebreathing exhaled air (e.g. from a paper bag) or holding one’s breath. The primary adverse effect of carbogen inhalation is a concentration- and duration-dependent sense of an increasingly urgent desire to breathe, or “air hunger”. Brief inhalations of higher concentrations of carbon dioxide (9–35% CO_2 in air) have been used as an experimental model of panic attacks. In one study [33] healthy volunteers inhaled two successive maximally deep breaths of various CO_2/air mixtures and rated maximum panic-related symptoms on a visual analogue scale. Symptom severity peaked rapidly and were reported retrospectively 60 seconds after the end of the inhalation. 9% CO_2: air inhalation (the lowest examined) resulted in no significant difference in panic score (visual analogue scale 0–100; 18.6±26.1 vs 16.1 ± 17.7).

Prolonged periods of 5% carbogen inhalation in healthy volunteers are well tolerated [30]: p_aCO_2 levels were 30% ±17% higher than when breathing air. Periods of up to 30 minutes of carbogen have been used as an adjunct to radiotherapy for glioblastoma multiforme in adults [34] and were well tolerated, as was a protocol of 30 mins inhalation four times daily in idiopathic sudden hearing loss (n=66) [35]. In one paper discussing use of 5% carbogen as an adjunct to radiotherapy in children with high grade brainstem gliomas some younger children (median 5 years, range 4–6) did not tolerate prolonged (4 and 6 minute) periods of inhalation because of resulting breathlessness [36]. They were however intrinsically very unwell. The older children in the study (median 11 years, range 7–15) had no problems.

The following are expected undesirable effects of 5% carbogen inhalation and constitute mild, expected ARs (see the Medical Gas Data Sheet (MGDS), which includes the Summary of Product Characteristics [37]): tachypnoea, tachycardia, sweating, nausea, headache, and reported sensations of, or external impressions of air hunger (breathlessness, anxiousness). Note however

that these latter subjective sensations require preserved awareness: they are unlikely to be relevant to children experiencing CSE and/or receiving sedating doses of benzodiazepines.

Summary of rationale

Manipulation of brain pH may be a neglected approach to termination of CSE, particularly in febrile CSE which is responsible for a high proportion of paediatric CSE. Carbogen provides a straightforward means of manipulating brain pH in the context of CSE. Adding carbogen to the current management of CSE may be a useful adjunctive treatment, improving first-line treatment response rates.

5.3 Risks and Benefits

Potential benefits

As most anticonvulsants used in the treatment of CSE have sedating or anaesthetic properties, respiratory complications are common. In contrast, carbogen is non-sedating, and if anything, a respiratory stimulant (the Carbogen Medical Gas Data Sheet [37] lists stimulation of respiration after periods of apnoea as a therapeutic indication). It is potentially both rapidly acting (in rodents, suppression of electrical seizure activity was seen within 30 seconds and was maximal within 5 minutes of p_aCO_2 reaching 6kPa [19]) and rapidly reversible. Seizure termination in rodents with carbogen is associated with a fall in extracellular pH of 0.2 units. The calculated associated intracellular shift would be -0.04 units (data on file). ^{31}P-MRS data (reflecting intracellular pH_i *in brain*) in healthy human volunteers confirms that 5% carbogen inhalation achieves an adequate ΔpH_i from 7.02±0.006 to 6.96±0.001 pH units [21, 38].

Potential risks

Although modest effects of physiological hypercapnia on cardiopulmonary and cerebrovascular physiology are reported [39] these will be dominated by the effects of the CSE. Increasing $FiCO_2$ would be predicted to cause (i) a respiratory acidosis (counteracted by a secondary metabolic alkalotic response) and (ii) increases in cerebral blood flow (CBF). The severe systemic lactic acidosis consistently observed in CSE is due to sustained anaerobic contraction of peripheral muscles (it does not occur when seizures are provoked under general anaesthesia in ECT [23]). In adults, systemic pH can fall as low as 6.8 and p_aCO_2 can reach 8kPa in severe CSE and can persist for up to an hour [40, 41]. In comparison, measured p_aCO_2 values in healthy adults breathing 5% carbogen under normal conditions were reported to be a mean p_aCO_2 of 6kPa (range 4.5–6.8 kPa) [42]. In our small pilot study in non-convulsive status (with no significant muscle contraction) no statistically significant changes in capillary pH before and after 120 seconds of 5% carbogen inhalation were detected [43].

Similarly, CBF is tightly autoregulated and very sensitive to p_aCO_2. Breathing 5% carbogen under normal conditions leads to a p_aCO_2 of up to 6.8 kPa [42] which might be expected to cause a ΔCBF of up to 20% [44]. This is negligible compared to the ΔCBF due to the seizure, which can increase by 100% even in brief focal seizures [45, 46] and several-fold in generalised seizures [47–49].

The MGDS [37] lists no contraindications to carbogen therapy. It states that “no overdose effects are seen with 5% carbon dioxide/oxygen medical gas mixture” but emphasises that the resulting acidosis will affect the “uptake and distribution by [*sic*] many drugs including neuromuscular

blocking agents and hypotensive agents", and "will interact with anaesthetic agents when the concentration is raised and gives rise to cardiac dysrhythmias. The threshold for dysrhythmias varies with different drugs". Again, these effects are due to the acidosis and are not specific to carbogen *per se*. Since acidosis is an established feature of CSE the extensive experience confirming the safety and tolerability of the medications used in the early management of CSE (first line benzodiazepines and second line treatments including phenytoin and levetiracetam) implies that these medications will also be safe to use concurrently with carbogen.

Two issues regarding *potential (false positive) misdiagnosis of CSE* require specific consideration as they may result in inadvertent enrolment in the trial.

1. One condition sometimes misdiagnosed as CSE is Non-Epileptic Attack Disorder ("pseudo-status epilepticus"), i.e. the generation of vigorous movements (but with fully-preserved awareness and variable insight and intentionality) of body and limbs, typically as a result of psychological distress, that can be mistaken for CSE. Although such misdiagnosis is regrettable as it exposes sufferers to medications and procedures (such as RSI) that are unjustified, and potentially entrenches a misdiagnosis of epilepsy, there are no reasons to expect that enrolment in CRESCENT should pose any increased risk additional to the mis-application of APLS treatment pathways.

2. One very rare scenario requires specific consideration. Severe neurological disease associated with severe swelling of the brain or other intracranial structures can result in a phenomenon known as brain herniation where pressure differential between different parts of the brain results in displacement of brain structures through various anatomical openings. Severe herniation is informally referred to as "coning", where the brain starts to displace down through the foramen magnum at the base of the skull. Brain herniation syndromes are recognised clinically by characteristic sustained postures of the limbs referred to as decorticate and decerebrate posturing. Anecdotally, such posturing has occasionally been mis-diagnosed as CSE and treated as such along APLS or similar pathways. As discussed, the benzodiazepines typically used as first line CSE treatment cause respiratory suppression, and thus elevation of p_aCO_2 and, as discussed above, thus elevation of intracranial pressure via increased CBF which in this context would aggravate the problem and potentially worsen the outcome. CRESCENT creates the possibility that such a misdiagnosis may occur and the child be given carbogen compounding the situation even further.

   There are usually strong clinical pointers to this scenario (e.g. clear history of recent severe head trauma, or prolonged prodrome of decreased consciousness) however the importance of the differential diagnosis of CSE will be a feature of the training offered as part of CRESCENT setup.

Being 95% O_2, the contents of a carbogen cylinder represent a fire hazard but cylinders will be stored using the same procedures as portable oxygen cylinders. The cylinders are smaller than those typically used in hospitals.

This trial is categorised as Type B as per the risk-adapted approach to clinical trials adopted by the MHRA.

5.4 Objectives

To ascertain (i) the effectiveness of carbogen in enhancing response rates of conventional first-line treatments of CSE and (ii) its safety in this context.

5.4.1 Exploratory Objectives

To determine whether the response to carbogen is modified by whether blood pH is more alkalotic.

To determine whether the response to carbogen is modified by whether the presenting seizure is a febrile CSE episode.

6 STUDY DESIGN

CRESCENT is designed as a randomised, placebo-controlled, double-blinded multicentre superiority trial with 1:1 allocation ratio.

The trial will be randomised and blinded to both participants and treating clinicians to avoid potential selection, performance and detection bias. Attrition bias will be minimised by analysing data based on the principle of intention-to-treat (ITT).

6.1 Blinding

The comparator in this trial (100% O_2) would normally be administered via the ED's fixed, piped oxygen supply infrastructure. To maintain blinding in the trial, both the comparator and the IMP (5%CO_2: 95%O_2) are delivered in identically-overpainted, small, CD size, medical gas cylinders. Trial intervention is for the first 10 mins from admission to ED. After 10 mins if required, oxygen can be delivered at the treating physician's discretion from the hospital piped oxygen supply, alongside ongoing APLS-guided medical treatment of CSE.

Individual cylinders will be numbered to permit identification of content. The lookup table allowing breaking of the blind for an individual cylinder will be held by LCTC but the protocol does not provide for emergency unblinding (see section 8.10).

No issues regarding taste, smell or other factors that might break blinding are anticipated.

In relation to regulations for the transportation of hazardous materials by road (ADR) both active and comparator cylinders will be labelled as "Compressed Gas Oxidising" (UN 3156).

6.2 Trial Setting

Participants will be identified and recruited from paediatric EDs in hospitals that contributed effectively to EcLiPSE. We intend to open approximately 12 sites, emphasising sites that were strong recruiters to EcLiPSE.

6.2.1 **Selection of Participating Sites**

Criteria for the selection of sites will be determined by the Trial Management Group. Sites will be asked to complete a feasibility criteria survey to determine their suitability.

Sites must have capacity to run the trial, be research experienced and have suitable storage facilities to store the trial cylinders.

Sites fulfilling the criteria will be selected and will open to recruitment upon successful completion of all global (e.g. REC and MHRA) and study-specific conditions (e.g. site personnel training requirements) and once all necessary documents have been returned to the LCTC. PIs must provide evidence of GCP certification. Initiation of sites will be undertaken in compliance with LCTC internal processes. Conditions and documentation required will be detailed on a LCTC Green Light Checklist maintained in the TMF and must be fully completed prior to opening sites to recruitment.

6.2.2 **Selection of Principal Investigators**

PIs will be required to have equipoise, relevant experience and commitment during early stage feasibility assessment. All investigators will have the particular medical expertise necessary to conduct the study in accordance to the protocol and all regulatory and ethical requirements. Written agreement to conduct research as such will be obtained prior to site initiation.

A suitable sub-investigator will be identified at each site to deputise in case of PI absence.

7 ELIGIBILITY CRITERIA

The CRESCENT trial aims to recruit 424 patients based on sample size calculations described in section 12. To be randomised, patients must meet all eligibility criteria as described below.

7.1 Inclusion Criteria

Patients eligible for the trial must comply with all of the following at randomisation:

1 Presenting to the paediatric Emergency Department (ED) of a participating site

2 Exhibiting signs of Convulsive Status Epilepticus (CSE) (i.e. ongoing generalised tonic-clonic, generalised clonic or focal clonic convulsive seizure activity) requiring – in the view of the treating physician - emergency treatment either according to standard APLS guidelines or the child's personalised rescue care plan[1] in order to try and terminate the presenting seizure

7.2 Exclusion Criteria

Any patient meeting any of the criteria listed below at baseline will be excluded from study participation:

1 Known to have been previously enrolled in CRESCENT

2 Infantile spasms (West Syndrome)

3 Non-epileptic seizure ("pseudo status epilepticus") (see section 5.3)

4 Tonic posturing due to suspected brain herniation (see section 5.3)

5 Has received phenytoin, levetiracetam, phenobarbital or valproate as part of the management of this episode of status epilepticus

Known or suspected pregnancy is not an exclusion criterion: see section 11.8 for further discussion.

Knowingly randomising patients who do not meet the eligibility criteria is not permissible and is in breach of Regulation 29 (SI 2004/1031) of the Medicines for Human Use (Clinical Trials) Regulations 2004 as amended.

[1] Some patients with established epilepsy will have CSE treatment plans that have been individualised and adapted in light of prior experience of response to standard APLS treatment protocols. Personalised plans occasionally make use of paraldehyde as an alternative, rectally administered, medication that is not part of standard APLS protocols. These children remain eligible for CRESCENT. For trial purposes paraldehyde is considered a first line medication.

7.3 Co-enrolment Guidelines

Although in general co-enrolment in multiple studies is to be avoided, the emergency nature of enrolment into this study precludes systematic enquiry as to whether individuals have or are currently participating in other Clinical Trials of Investigational Medicinal Products (CTIMPs). The physiological effects of carbogen inhalation are very short term and there are no grounds for believing there are any physiological effects persisting more than a few minutes from the end of inhalation. Involvement in additional studies within 30 days of enrolment in CRESCENT will need to be discussed with the LCTC who will contact the CI (Dr Rob Forsyth).

8 TRIAL TREATMENT/INTERVENTIONS

8.1 Introduction

Eligible patients will be randomised 1:1 between carbogen and oxygen arms. All patients will receive standard pharmacological management of CSE according to APLS guidelines (modified where applicable in individual emergency seizure treatment plans) whilst inhaling 100% Oxygen or Carbogen (5%CO_2: 95%O_2) delivered at 15 litres/min for the first 10 mins of treatment.

To maintain blinding during the first 10 minutes the inhaled gas will be delivered from a single-use "CD" size medical gas cylinder (length 52cm, diameter 10cm; weight 3.5kg; capacity 400 litres). After 10 minutes, if the treating physician judges further oxygen administration to be necessary (alongside any ongoing treatment of CSE) this is delivered (open label) from the hospital piped-oxygen supply.

IMP will be supplied and packaged by British Oxygen Company (BOC) in accordance with all applicable guidelines.

8.2 Treatment Description

8.2.1 **Carbogen arm (intervention)**

Brand name / Active ingredient:	Carbogen®; 5%CO_2: 95%O_2
Formulation:	Medical gas
Manufacturer:	BOC
Packaging, storage and stability:	Delivered in painted light blue (to indicate that they are oxidising gases), single-use "CD" size cylinders with affixed regulator valve. Refer to Pharmacy Manual for storage requirements
Supplier's name:	BOC
Regulatory Status:	Market Authorised (off licence indication)

8.2.2 **Oxygen arm (control)**

Brand name / Active ingredient:	100% O_2
Formulation:	Medical gas
Manufacturer:	BOC
Packaging, storage and stability:	Delivered in painted light blue (to indicate that they are oxidising gases), single-use "CD" size cylinders with affixed regulator valve. Refer to Pharmacy Manual for storage requirements
Supplier's name:	BOC
Regulatory Status:	Market Authorised

8.3 Manufacturing and Distribution

IMP cylinders will be distributed to sites in batches of consecutively numbered cylinders. These identifying numbers will be large and highly visible. Additional batches will be supplied as required when remaining stock reaches an appropriate threshold.

Cylinder Preparation

BOC will create the recipes for the two gas mixtures on BOC's Production Order System, to include cylinder preparation information as well as filling instructions and batch result record sheets, and review and approve recipes for the Trial. Annex 13-compliant clinical trial labels will be finalised and approved and a single internal BOC product code will be assigned for both mixtures.

Cylinder labels, including a unique cylinder-identifying bar code for each cylinder, will be printed. Cylinders will be prepared and painted light blue at BOC's Wolverhampton Test Shop. Standard Medical Oxygen Integral Valves will be fitted to tested cylinder shells and the body labels and external transparent plastic protection sleeves will be fitted to the cylinders. The cylinders will be registered on a database (unique bar code/cylinder number/valve number) and transported to BOC Morden.

Trial Preparation

BOC will raise production orders for batches of cylinders (carbogen and oxygen) and filled cylinders will be quality control checked and stored in a quarantined area. The batch records will be signed off by a Qualified Person (QP) and a certificate prepared and sent to the LCTC.

Initial Clinical Trial Supply

As orders are received from LCTC, the BOC Designated Person will label each cylinder according to the randomisation sequence for each site supplied by LCTC. BOC trial records will record the content and cylinder labelling of each cylinder (identified by its unique bar code).

BOC will complete their Clinical Trial Records to record the Production Order No, the actual gas filled, the filling date and the individual cylinder bar code. This record will be updated as and when cylinders are allocated to a specific trial site.

BOC will deliver an initial opening supply to each trial site, recording bar codes delivered.

Cylinder resupply

Trial sites will notify LCTC when replenishments are required, LCTC will notify BOC and BOC will raise a new production order. BOC will fit clinical trial site labels and randomisation number labels as per the randomisation sequence, deliver new cylinders to site and collect empties. Empty cylinders will be quarantined at the Morden depot. Stock management and reconciliation will be performed at Morden.

8.4 Preparation, Dosage and Administration

Storage of unused trial cylinders

Cylinders will be stored at each hospital at ambient temperature in designated and appropriately ventilated medical-gas storage areas as close to ED as possible. Cylinders will be used in sequence as per the identifying cylinder number. The lowest-numbered cylinder for use will be stored in the ED Resuscitation Bay or equivalent location in anticipation of the next eligible child's arrival.

Storage of used trial cylinders

Upon completion of enrolment of a patient, the partially-used cylinder will be quarantined and the next consecutively-numbered cylinder brought out of store in anticipation of the next recruitment. This will be completed as soon as feasible to minimise the risk of being unprepared to enrol a new patient presenting soon after a previous enrolment.

Dose and administration

IMP is delivered by non-rebreather face mask attached by elastic at 15 litres/min to minimise the risk of dilution of the IMP by entrainment of room air during inspiration. Inhalation is for 10 mins.

Early termination of treatment

Two situations of possible early termination of treatment are foreseen:

1. A child becomes more aware of their circumstances (e.g. because of early termination of CSE), is distressed and pulls off the mask.

2. Respiratory depression is an important complication of current treatment of CSE (particularly if excessive administration of parenteral benzodiazepines has occurred). Occasionally treating teams will institute temporary, manual ventilatory support in an attempt to stave off formal intubation and ventilation. Typical forms of support include AMBU® bags or equivalent, or *circuits* such as a Mapleson F ("T-piece") and Mapleson C (in larger adolescents). These devices can be attached directly to a cylinder supply and thus IMP can continue to be delivered. However, some alternatives such as Circle Systems can only be driven via an anaesthetic machine and so cannot be attached directly to an IMP cylinder. Circuits would only be used by appropriately trained medical practitioners (typically anaesthetists or intensive care physicians). The need for such respiratory support increases with duration of treatment and number of administered benzodiazepine doses and is anticipated to be infrequent in the first 10 mins of treatment but can be instituted as deemed necessary by treating physicians, if necessary terminating the use of the IMP before 10 mins has elapsed.

In these and in all similar circumstances, data collection should continue and analysis will be on an intent-to-treat basis.

8.5 Treatment Modifications

Due to the very short period of active participation in the trial and the similar nature of the treatments in each arm, treatment modification is not anticipated to be an important issue. However, the clinician is free to give alternative treatment to that specified in the protocol at any

stage, if s/he feels it to be in the best interest of the patient: in particular the physician may choose to switch from inhalation of medical gas from the study cylinder to the hospital piped-oxygen supply. However, the reason for doing so should be recorded on the CRF and the patient will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated.

8.6 Accountability Procedures

Accountability logs will be held at each site to record:

1. receipt of cylinder consignments from BOC to central stores
2. transfer of cylinders from central stores to the ED-adjacent medical gases storage area (as much of a site's stock should be stored in ED as space permits at any one time to avoid inadvertent out-of-hours outages)
3. return of used cylinders to central stores
4. return of used cylinders to BOC

The pharmacy manual provides further detailed guidance for pharmacy departments.

8.7 Assessment of Compliance

Treatment with the IMP will be administered under the direct supervision of a clinician and in a controlled clinical environment; therefore, full assessment of compliance is anticipated in this trial. Confirmation of completion of 10 mins inhalation as intended, or the occurrence of early discontinuation (e.g. due to the scenarios discussed in section 8.4) will be recorded in the CRF.

8.8 Concomitant Medications/Treatments and Specific Restrictions

There are no restrictions in relation to concomitant medication or treatments. The following data on concomitant medication will be recorded on the CRF:

- Benzodiazepines administered prior to randomisation (i.e. pre-admission)
- Pre-admission epilepsy medication
- The use of other first-line and second-line drugs to treat the seizure

8.9 Overdose

The delivery of medical gas (100% O2 or 5%CO_2: 95%O_2) at 15 litres/min is intended to provide a large excess of the gas at the mouth and nose so as to preclude dilution by entrainment of room air even with a high inspiratory flow rate (e.g. a gasp). These thus represent the highest values of inspired O_2 and CO_2 possible. The gas is delivered via a standard, non-rebreathing, facemask. Any mixing with room air will result in F_iO_2 and F_iCO_2 values nearer those of air (~21% and ~0.04% respectively). Thus, overdose is not possible in the context of this trial.

8.10 Unblinding

There is no emergency unblinding process for participants randomised into CRESCENT. The composition of gases in lungs and blood re-equilibrates extremely rapidly (within seconds) of reversion to spontaneous or assisted ventilation in air or another inhaled gas mixture. For this reason, there is no need to unblind a participant's allocation contemporaneously. Knowledge of the IMP received would not change the medical management (which would continue according to APLS principles) and any unblinding process would introduce unnecessary delays into the management of an emergency situation.

8.10.1 **Accidental Unblinding**

All accidental unblinding must be documented appropriately according to LCTC processes. If accidental unblinding occurs at site research staff at site should contact the Trial Manager as soon as possible. Where necessary, the TMG will review incident reports and determine if preventative actions are required.

9 OUTCOMES

9.1.1 Primary Outcome

Success of first-line treatment of CSE (i.e. child did not need to receive second-line or rescue therapy as defined within the APLS guidelines or their personal treatment plan). Success of first line treatment is defined as not requiring intravenous phenytoin, phenobarbital, valproate, levetiracetam, or RSI.

9.1.2 Secondary Outcome(s)

- Seizure activity visible at 5 minutes and 15 minutes post commencement of inhalation
- Need for rapid sequence induction (RSI) with thiopentone or another agent (e.g. propofol) due to ongoing CSE
- Need to be admitted to critical care (PICU) or high dependency unit
- Seizure recurrence within 24 hours
- Serious adverse events and reactions
- 30-day mortality

Objectives	Outcome Measures	Timepoint(s) of evaluation
Effectiveness:		
Whether concurrent carbogen use increases response rates to first line treatment of CSE	Success of first-line treatment of CSE (i.e. child did not need to receive second-line or rescue therapy as defined within the APLS guidelines or their personal treatment plan). Success of first line treatment is defined as not requiring intravenous phenytoin, phenobarbital, valproate, levetiracetam or RSI	At 24 hours
	Seizure activity visible at 5 minutes, and 15 minutes post commencement of inhalation	At 5 minutes and 15 minutes post commencement of inhalation
	Need for rapid sequence induction (RSI) with thiopentone or another agent (e.g. propofol) due to ongoing CSE	At 24 hours
	Need to be admitted to critical care or high dependency unit	At 24 hours
	Seizure recurrence within 24 hours	At 24 hours
Safety:		
Ascertain the safety of carbogen	Serious adverse events and reactions	From randomisation up to 30 days, with an onset within 24 hours of inhalation
	Mortality within 30 days of enrolment	Identified retrospectively

10 PARTICIPANT TIMELINES AND ASSESSMENTS

10.1 Participant Identification

Participants are identified as they arrive in ED in CSE (or develop CSE in ED). In most if not all cases the treating clinician will deem that the episode of CSE requires medical treatment to terminate. The likeliest grounds for *not* immediately commencing emergency treatment is if the episode of CSE is known to be short (e.g. the onset was observed in ED) or the episode of CSE appears to be self-resolving (amplitude and frequency of convulsive movements declining) on first medical assessment. As discussed in section 5.3 there are two conditions (non-epileptic attack or "pseudo-status"; and tonic posturing due to coning and herniation) that must be distinguished from CSE. Training on this issue will be provided as part of site opening and reiterated with change of "house".

10.2 Eligibility Assessment and Confirmation

Eligibility can only be confirmed by an appropriately qualified medical professional with the experience to manage CSE emergency situations (Emergency Medicine or Paediatric Consultant or Specialist Registrar on duty) who is named on the site delegation log. Due to the emergency nature of the condition fully informed consent is not required before eligibility is confirmed. Patients presenting to paediatric ED with generalised tonic-clonic, generalised clonic or focal clonic status epilepticus that requires first-line treatment will be assessed by clinical staff and randomised if they fulfil the eligibility criteria (see section 7).

Eligibility confirmation must be documented in the participant's medical notes and on the trial's Eligibility CRF (Form 1). Details must include who confirmed full eligibility, when this was confirmed, and when the participant was formally entered into the trial.

For the reasons described in section 14.2, no attempt will be made to obtain fully informed consent for the trial from the patient/parent/legal representative prior to randomisation. Please see section 10.3 for the deferred consent procedures

10.3 Baseline Assessments

Due to the emergency nature of the condition no baseline assessments are required before randomisation. The Follow-Up 0-24 hours CRF (Form 3) will collect retrospective data on estimated pre-admission seizure duration, and any pre-admission administration of emergency medication by family, teachers or paramedic crews.

10.4 Randomisation

The randomisation code list will be generated by a statistician (who is not involved with the trial) at LCTC that will inform the cylinder filling sequence for BOC (see section 8.3). Participants will be randomised to 5%CO_2: 95%O_2 or 100%O_2 in a ratio of 1:1. Clinicians and participants will be blinded to allocation. Identical cylinders will be prominently labelled with a randomisation number (for cylinders to be used in sequential order).

Following confirmation of eligibility, the cylinder with the lowest randomisation number should be used.

The small tear off randomisation number label on the cylinder should be removed by the ED staff and added to the CRESCENT Dispensed Form.

Sites must keep a randomisation log which lists the name of each patient randomised and their randomisation number. The randomisation log will remain at site and is only for site use.

10.5 Intervention

Randomisation and treatment allocation are in effect decided *before* the next patient presentation to ED. The randomisation determines the next medical gas cylinder (containing either 5%CO_2: 95%O_2 or 100%O_2) to be delivered to ED and retained there in anticipation of the next enrolment. Trial treatment commences immediately upon confirmation of eligibility.

10.6 Record of treatment provided in ED

The ED team must complete the Randomisation and Initial Treatment form (Form 2).

A member of the local CRESCENT research team will arrange to pick up the completed forms from the ED. They will store the completed CRFs and will provide the completed Dispensed Form to the pharmacy department at site.

10.7 Emergency Deferred Consent

As CSE is a medical emergency, participants will be treated according to the trial protocol prior to obtaining consent. This deferred consent model has been successfully used in a number of ED trials [51] and this was supported by qualitative research findings both before and during delivery of the trial [8].

Consent will be sought for all patients when their clinical condition has stabilised. Assent will be sought as appropriate from older children (i.e. 12 years and over).

The large majority of enrolled patients are anticipated to be under 16, since most over 16-year olds would be directed to adult ED on arrival, however it is possible that a 16, 17 or perhaps 18-year old presents at a paediatric ED and these patients will be eligible by virtue of their attending a *paediatric* ED. It is anticipated that young people with significant underlying neurodisability will be over-represented in this group and provision is made for the recruitment of an over 16-year old without capacity to consent. Over 16-year olds with capacity will be approached for deferred consent in their own right.

After confirmation of eligibility, randomisation, and completion of trial participation (i.e. completion of 10 mins inhalation of medical gas; and subsequent satisfactory resolution of the episode of CSE), deferred consent should be sought.

Anonymous data, for the purposes of the recipients, will be sent to the LCTC to allow monitoring of safety in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 as amended. Personal identifiable data will be subsequently sent to LCTC following written informed consent.

10.7.1 Approaching Parents/Legal Representatives/Participants

The RN, or other designated member of the research team at site, will be notified of the randomisation and will approach the person with parental responsibility/ legal representative/patient to seek deferred consent as soon as possible after completion of trial treatment (ideally within 24 hours of randomisation). See Section 10.7.5 for definitions of a legal representative.

Before approaching the parent/legal representative/patient, the RN will check with the relevant ward staff that the patient is stable and that timing is appropriate. If the patient's condition has not stabilised additional time should be allowed before approaching the parent/legal representative/patient. If the patient has died please refer to section 10.7.6.

A brief information leaflet is available for the situation where a parent or attendant with previous experience of CSE realises that this episode is being managed differently and raises this with ED staff. It acknowledges the trial, reassures the reader that it has been fully approved and that Research Staff will explain and provide information as soon as possible and appropriate.

10.7.2 Providing Trial Information

The RN, or other designated member of the research team at site will explain to the parent/legal representative/patient the reasons why deferred consent is used in emergency care research, and will discuss the objectives, risks and benefits of the trial. The parent/legal representative/patient will be provided with the appropriate Participant Information and Consent/Assent forms (PISCs) (see section 10.7.4) and will be asked to read and review these. They will be given opportunity to ask any questions that may arise, have the opportunity to discuss the study with others and have time to consider the information prior to agreeing to consent. A contact point where further information about the trial may be obtained will be provided.

The designated member of the research team should explain that anonymised data has been collected about the patient's seizure and treatment from the information in hospital notes. This data is anonymous for the purposes of the recipients (LCTC) and is processed to allow monitoring of safety. Permission will be sought for disclosure of pseudonymous and directly identifiable data. Parents/legal representatives/patient should decide ideally within 24 hours of randomisation or before the patient is discharged from hospital.

10.7.3 Consent/Assent Form Completion

If the parent/legal representative/patient agrees to disclose identifiable data they will be asked to sign and date the age-appropriate CRESCENT consent/assent forms (see section 10.7.4). The person obtaining consent/assent must then also personally sign and date the form.

A copy of the fully completed consent/assent form will be given to the parent/legal representative/participant for their records. The original copy will be filed in the Investigator Site file, with a copy in the participant's medical notes. Copies of the consent/assent form should also be sent to the LCTC.

10.7.4 Information Sheets, and Deferred Consent and Assent Forms

The applicable information sheets should be provided and the relevant consent forms completed.

In conjunction with informed consent for minors, the applicable information sheet should be provided and assent should be sought for children 12-15 years old where capacity allows.

Trial Participant Status	Documentation to be provided	Completed by
Children less than 6 years old	A. CRESCENT Parent/personal legal representative information sheet and deferred consent form OR B. CRESCENT Professional Legal Representative Information Sheet and Consent form	Researcher and: i A parent or person with parental responsibility. OR ii Personal legal representative* * OR iii Professional legal representative*
Children aged 6-11 years	A. CRESCENT Parent/personal legal representative information sheet and deferred consent form OR B. CRESCENT Professional Legal Representative Information Sheet and Consent form AND D. CRESCENT Child information sheet (6-11 years)	Researcher and: i A parent or person with parental responsibility. OR ii Personal legal representative* OR iii Professional legal representative*
Young persons (12 years and older) ***without*** capacity to assent or consent	A. CRESCENT Parent/personal legal representative information sheet and deferred consent form OR B. CRESCENT Professional Legal Representative Information Sheet and Consent form AND F. CRESCENT Young Persons Information Sheet (12 years and older) no capacity for assent or consent	Researcher and: i A parent or person with parental responsibility. OR ii Personal legal representative* OR iii Professional legal representative*

Trial Participant Status	Documentation to be provided	Completed by
Young People aged 12-15 years ***with*** capacity to provide assent	A. CRESCENT Parent/personal legal representative information sheet and deferred consent form OR B. CRESCENT Professional Legal Representative Information Sheet and Consent form AND E. CRESCENT Young person information sheet and deferred assent (12 years and over)	Researcher and: i. A parent or person with parental responsibility. OR ii. Personal legal representative* OR iii. Professional legal representative* Researcher, parent/legal representative* and trial participant
Young adults (aged 16 to 18 years) who, upon recovery from their seizure, **do not have** capacity to give informed consent ("incapacitated adults")	A. CRESCENT Parent/personal legal representative information sheet and deferred consent form OR B. CRESCENT Professional Legal Representative Information Sheet and Consent form AND F. CRESCENT Young Persons Information Sheet (12 years and older) no capacity for assent or consent	Researcher and: i. A parent or person with parental responsibility. OR ii. Personal legal representative* OR iii. Professional legal representative*
Young adults who, upon recovery from their seizure, **have** capacity to give informed consent	C. CRESCENT Young Adult (16 years and over) information sheet and deferred consent form	Researcher and trial participant
Bereaved parents/relatives	G. CRESCENT Parent/personal legal representative information sheet and deferred consent form (bereaved) OR B. CRESCENT Professional Legal Representative Information Sheet and Consent form	Researcher and: i A parent or person with parental responsibility. OR ii Personal legal representative* OR iii Professional legal representative*

*please refer to section 10.7.5 for definitions of legal representatives

Note: If the participant dies prior to deferred consent being sought refer to section 10.7.6

It is not feasible to provide a comprehensive set of PISCs in languages other than English because of the multiple age bands and capacities for assent involved, and the heterogeneity of locally-important languages other than English between recruiting sites. Where necessary trial information and approach for consent will be supported using hospitals' translators or telephone interpretation services. The study results will be translated into the languages spoken by those participants who do not speak English.

10.7.5 Definitions of Legal Representatives

For children and young people under 16 years in England, and for those adults lacking capacity a personal legal representative is a person not connected with the conduct of the trial who is suitable to act as the legal representative by virtue of their relationship with the minor, and is available and willing to do so.

If a personal legal representative is not available a professional legal representative will be used. This is a person, independent from the study, who is the doctor primarily responsible for the medical treatment of the minor or person over 16 years of age, or a person nominated by the healthcare provider. If the doctor primarily responsible for the medical treatment of the patient is the PI or a member of the CRESCENT study team, then they will not be considered independent and therefore will not be able to consent on behalf of the patient.

10.7.6 Death Prior to Deferred Consent being sought

Death in ED, or within 24 hours of presentation, is anticipated to be a very rare occurrence in this study population. However, when a participant dies the attending RN will obtain information from colleagues and bereavement counsellors to establish the most appropriate practitioner to notify parents/legal representative/s of the research involvement.

Deferred consent can be sought from parents/legal representatives following the death of their child/relative and prior to the parents/legal representative's departure from the hospital. However, it is at the discretion of the site staff to determine if this is appropriate. In this situation, Parent/Legal representative information sheet and deferred consent form (B) (Information sheet G) would be used.

If deferred consent is not sought prior to the parent/legal representative's departure from hospital the identified practitioner will call the parent/legal representative when deemed appropriate, to inform the family of the involvement in the trial.

Once the telephone call has been completed a personalised letter from the most appropriate practitioner (Parent/Legal representative bereavement letter, and a copy of the Parent/Legal representative information sheet and deferred consent form for bereaved parents (Information sheet G) will be sent to the parent/legal representative. As with a face-to-face appointment, the details of such discussions should be recorded within the medical notes.

If 8 weeks (56 days) after sending the letter to the bereaved family, there is no response, no further letters will be sent to the bereaved family. .

Where the parent/legal representative agrees to provide consent, the parent/legal representative should sign and date the consent form and return as instructed by the researcher. The practitioner who carried out the informed consent discussions should sign the consent form upon receipt. A copy of the fully signed consent form must be sent to the parent/legal representative for their records. The original should be filed inside the Investigator Site File (ISF) and a further copy of the

signed consent form will be filed with the medical notes. One final copy of the consent form should be sent to the LCTC.

In addition, all deaths should be reported on a Serious Adverse Event CRF and emailed to the LCTC within 24 hours (see section 11).

10.7.7 Discharge/Transfer Prior to Deferred Consent being sought

It is expected that deferred consent is sought for **all** patients prior to discharge/transfer to another hospital (if the patient dies prior to consent being sought refer to section 10.7.6). However, in rare instances where deferred consent is not sought prior to discharge/transfer the following should occur:

The RN, or other designated member of the research team at site, will call the participant/parent/legal representative (using a telephone interpreter if required) via telephone or video conference (that are in line with local trust requirements/policies) within 5 working days of randomisation to inform the family of the patient's involvement in the trial and provide details of the trial as per section 10.7.2). As with a face-to-face appointment, the details of such discussions should be recorded within the medical notes.

Once the telephone call has been completed, the RN, or other designated member of the research team at site, will send (within 5 working days) the appropriate covering letter and PISC appropriate to the patient's age and capacity status.

If after three attempts, telephone contact has not been possible, the appropriate covering letter and PISC will be sent to the participant/parent/legal representative.

The covering letter will confirm that the patient/parent/legal representative has 4 weeks from the date of the letter to return the consent form if they provide their consent.

Where the patient/parent/legal representative agrees to consent, the patient/parent/legal representative should sign and date the consent form and return as instructed by the researcher. The researcher who carried out the informed consent discussions should sign the consent form upon receipt. A copy of the fully signed consent form must be sent to the participant/parent/legal representative for their records. The original should be filed inside the ISF and a further copy of the signed consent form will be filed with the medical notes. One final copy of the consent form should be sent to the LCTC.

In the event of a non-response a reminder phone call will be made and if necessary further copies of the covering letter and PISC posted.

10.7.8 Action in event of lack of response to written approaches for consent with reminders

If no response is received within 4 weeks (28 days) of the second reminder letter or 8 weeks (56 days) of the letter for bereaved families, no personal identifiable data (PID) will be sent to the LCTC. The LCTC will monitor safety and analyse the anonymous data provided only.

10.7.9 Deferred Consent Declined

If deferred consent is *declined* by the appropriate parent/legal representative this should be noted in the 30-day CRF. No personal identifiable data (PID) will be sent to the LCTC. The LCTC will monitor safety and analyse the anonymous data provided only.

10.8 Schedule for Assessments and Follow-up

All follow up and outcome data is obtained by researchers from case notes. There are no additional assessments, questionnaires or visits required of participants. Follow-up is complete 30 days after randomisation. A designated member of the local CRESCENT research team will complete the 0-24 hours CRF (Form 3), at least 24 hours after randomisation and the 30-day CRF (Form 4) at least 30 days after randomisation.

Assessments and follow up are to be conducted in line with the Schedule of Assessments below:

	Emergency Department *Eligibility and Randomisation*	**0-24 hours** *After randomisation*	**30 days** *After randomisation*
Informed consent (deferred)		X	
Confirmation of eligibility criteria	X		
Randomisation	X		
Time of seizure onset from parent/relative recall	X		
Visible seizure activity at 5 minutes and 15 minutes (recorded in real time by attending clinician)	X		
Study intervention including compliance	X		
Need for emergency drug treatment and further management for the presenting seizure	X		
Need for RSI (recorded in real time by attending clinician)	X		
Participant details (including age, ethnicity and sex)	X		
Admission blood gas pH and sample type (recorded in real time by attending physician)	(X)		
Details of presenting seizure		X	
Time of seizure onset from 999 call if available		X	
Cause of presenting seizure		X	
Medical history including epilepsy (abstracted from notes by Research Nurse or equivalent)		X	
Maintenance anti-epilepsy drug regime at time of seizure presentation (abstracted from notes by Research Nurse or equivalent)		X	
Record of further seizures including treatment and further management in the first 24 hours after the first presentation		X	
Initial transfer out of ED including patient location at 24 hours		X	
Confirmation of CSE diagnosis			X
Hospital Discharge status			X
Mortality			X
Consent status			X
Serious Adverse Events/Reactions	X	X	X

(X) if collected routinely

10.9 Sampling

An admission “blood gas” estimation is typically performed as part of standard clinical care in management of CSE. The blood sample may variously be arterial, venous or capillary in origin depending on the available access. In an ED emergency situation venous or capillary samples are most probable.

This protocol *does not stipulate* that a blood gas sample should be obtained but where performed, the time of the sample, the measured blood pH and whether the sample is of capillary or venous origin will be recorded in the CRF.

10.10 Intervention Discontinuation and Participant Discontinuation/Withdrawal

Given the very short duration of the intervention, intervention *discontinuation* at participant/parent/legal representative request is not anticipated.

Clinician-led treatment discontinuation is permitted if there is any change in the study participant’s condition that justifies the discontinuation of treatment in the clinician’s opinion. Follow-up data should continue to be collected.

The participant/parent/legal representative is free to withhold or withdraw consent at any time without providing a reason (although the reason will be recorded if given) and without being subject to any resulting detriment. The rights and welfare of the patients will be protected by emphasising to them throughout the trial that the quality of medical care will not be adversely affected if they decline to participate in the study.

Where the participant/parent/legal representative wishes to withdraw consent a withdrawal CRF should be completed within 7 days and sent to LCTC documenting the reason for withdrawal.

Any SAEs and SARs will be notifiable to LCTC via processes detailed in section 11 even if a participant has withdrawn.

A minority of patients may also be randomised and treated at a CRESCENT site and then transferred to another hospital for further treatment before the follow up period is complete (e.g. the participant needs to be transferred to a hospital with a PICU). In these cases, the initially-treating hospital should contact the receiving hospital to collect the follow up information and consent (where possible).

Note: Only receiving sites that are recruiting sites for CRESCENT can assist with the consent process, however, regardless of where consent was sought, the patient would be classified as a recruited patient for the initially-treating site only.

10.11 End of Trial

The end of the trial is defined to be the date on which data for all participants is frozen and data entry privileges are withdrawn from the trial database. The trial may be closed prematurely by the Trial Steering Committee (TSC), on the recommendation of the Independent Data and Safety Monitoring Committee (IDSMC).

The trial may also be closed prematurely as a result of the formal Interim Analysis planned at the 12 months milestone (see section 12.3)

Site and closure activities will be centrally coordinated and conducted in accordance with LCTC processes regardless of whether the trial closes as planned or prematurely. This includes activities such as:

- End of Trial notification to REC and MHRA.
- Trial-related materials reconciled and returned/disposed of as appropriate see section 8.6 for IMP.
- All site data entered onto the study database, discrepancies raised and satisfactory responses received.
- Quality Control checks of the Investigator Site Files, Pharmacy Files and Trial Master File as appropriate.

11 SAFETY REPORTING

Safety reporting in clinical trials is a legal and ethical requirement and it is imperative that all applicable requirements detailed here are followed during the trial.

11.1 Terms and Definitions

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be *any* unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, *whether or not* considered related to the medicinal product.

Adverse Reaction (AR)

Any untoward and unintended *response* to an investigational medicinal product (i.e. caused by the IMP).

Serious Adverse Event (SAE)

Any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Serious Adverse Reaction (SAR)

An adverse reaction which also meets the definition of serious (above, and section 11.2) is a Serious Adverse Reaction. A Serious Adverse Reaction event that has been assessed as ‘expected’ (see section 11.5) according to the Reference Safety Information (see below) will remain classified as a Serious Adverse Reaction only, however Serious Adverse Reactions that are considered ‘unexpected’ will be further classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR) (see below).

Suspected Unexpected Serious Adverse Reaction (SUSAR)

An adverse reaction that is classed in nature as serious and “unexpected” (i.e. not listed within the Reference Safety Information approved for the trial by the MHRA and current at the time of onset of the SUSAR).

Reference Safety Information

The Reference Safety Information is used for assessing whether an adverse reaction is expected (see section 11.5). For medical gases the Medical Gas Data Sheet (MGDS) includes the Summary of Product Characteristics and must be approved for use by the MHRA. The Reference Safety Information used to assess the expectedness of a SAR must be the current approved version at the time of onset of the SAR. The Reference Safety Information for this trial is defined in section 11.5.1.

11.2 Assessment of Seriousness

The assessment of seriousness of safety events should be performed by an appropriately delegated, medically qualified member of the site research team.

A safety event/reaction is assessed as serious if it:

- Results in death
- Is life threatening (i.e. the investigator considers the event places the subject at immediate risk of death from the experience as it occurred (this does not include an adverse experience that, had it occurred in a more severe form, might have caused death)
- Results in an unanticipated hospitalisation or prolongation of hospitalisation
- Results in persistent or significant new disability or incapacity not present prior to enrolment
- Consists of a congenital anomaly or birth defect (in offspring of subjects taking the IMP regardless of time of diagnosis)
- Caused other important medical events (these may not result in death, be life-threatening, overdose, secondary malignancy or require hospitalisation, but may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition)

Note that hospitalisation and/or PICU admission for treatment of the episode of CSE *per se* (including rapid sequence induction of general anaesthesia) and/or support for respiratory depression associated with its treatment NEED NOT be regarded as serious if, in the view of the treating physician, the clinical course is typical of CSE and its management. The decision to regard hospitalisation and/or PICU admission as indicative of a "serious" AE/AR is at treating physician's discretion.

11.3 Severity of Adverse Events

All adverse events should be assessed for severity. Standard criteria for this are based on impact on routine activities (see Table 1).

Table 1: Severity Grading

Severity	Description
Mild	Does not interfere with routine activities.
Moderate	Interferes with routine activities.
Severe	Impossible to perform routine activities.
Life-Threatening	
Death	

N.B. A distinction is drawn between **serious** and **severe** AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 11.2. Hence, a severe safety event need not necessarily be a "serious" safety event.

11.4 Assessment of "Causality": Relationship to Trial Treatment

The assignment of the causality should be made using the definitions in the table below:

Table 2: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given
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 trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Events that are assessed as being possibly, probably or almost certainly related will be reported as having a reasonable possibility of being related, and events assessed as unrelated or unlikely will be reported as having no reasonable possibility of being related.

Assessment of causality should be made based on the known safety profiles of carbogen and oxygen. If any doubt about the causality exists the local investigator should inform the LCTC who will notify the Chief Investigator. In the case of discrepant views on causality between the treating investigator and others, the opinion of the treating investigator will never be downgraded and the MHRA and REC will be informed of both points of view.

11.5 Assessment of "Expectedness"

The Chief Investigator for the CRESCENT trial is responsible for determining whether a safety event is expected or unexpected, however a Chief Investigator will not assess their own patients, these patients will be assessed by the Medical Reviewer. There is no requirement for a reporting investigator to make an assessment of expectedness.

An event will be considered unexpected if it is not listed within the Reference Safety Information (section 11.5.1) for the study current at the time of the event's onset (note also the comment about PICU admission for treatment of CSE, see section 11.2). The nature, severity, or frequency of the

event should be considered – if this is not consistent with that described for the type of event in the Reference Safety Information the event should be assessed as unexpected.

11.5.1 Reference Safety Information

The Reference Safety Information for Oxygen is section 4.8 of the Compressed Medical Oxygen Medical Gas Data Sheet produced by BOC.

The Reference Safety Information for Carbogen is section 4.8 of the 5% carbon dioxide/oxygen medical gas mixture Medical Gas Data Sheet produced by BOC.

11.6 Time Period for Active Monitoring of Safety Events

IMPORTANT: Any safety events occurring after the end of the below described "active monitoring" period which meet the definition of serious (see section 11.2) and are recorded for this study must continue to be reported by sites to the LCTC in accordance with the timeframes and procedures described in section 11.11. The same processes established for SAEs within the active monitoring period should be followed for these events.

Active monitoring of safety events experienced by trial participants will be for 30 days from randomisation, but limited to only serious events or serious reactions with an onset within 24 hours of the initial inhalation. Safety will be assessed by the Principal Investigator (PI) or delegated research staff monitoring and reporting all serious adverse events and serious reactions from randomisation during this period. If a recruited participant is transferred to another hospital, then follow up with the accepting hospital should be completed to ensure that the data recorded are accurate.

30-day mortality will be ascertained by sites by reviewing the medical notes.

Pregnant women will be followed up until the outcome of the birth (see section 11.8 for more information on reporting pregnancy).

11.7 Notes on Safety Event Recording

The CRESCENT trial will only record and report Serious Adverse Events (SAEs) and Serious Adverse Reactions (SARs) with onset within the first 24 hours following inhalation. These should be reported according to the flowchart in section 11.11. Due to the very short-lived nature of the pH perturbation caused by carbogen inhalation adverse events with *onset* >24 hours after inhalation are not collected.

The following events if assessed as serious must be reported for the purposes of the trial:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event/condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or symptoms present at baseline that worsens following the administration of the study/trial treatment
- Laboratory abnormalities that require clinical intervention or further investigation (unless they are associated with an already reported clinical event).

- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention
- Injury or accidents
- Pregnancy (see section 11.8 for more details)

11.8 Reporting of Pregnancy

The likelihood of pregnancy in the CRESCENT study population is very low. This is because of the age (large majority pre-pubertal) and characteristics (increased rates of epilepsy-associated co-morbidities including learning difficulties, cerebral palsy and autistic spectrum disorder) of the patient population. Enquiry as to the possibility of pregnancy would delay effective treatment and would not be part of standard care for CSE. Treatment will not be delayed in order to undertake a pregnancy test.

Even if known to be pregnant on arrival young women will be enrolled. As discussed elsewhere (see section 5.3) 5%CO_2: 95%O_2 inhalation involves no exposure to novel or "extrinsic" molecules: it causes perturbations of acid-base status and elevations of p_aCO_2 of a magnitude probably smaller than those of the CSE itself. Teratogenicity is not a plausible concern. The risk to a pregnant woman is the known, significant morbidity for both mother and fetus associated with a CSE event in pregnancy [55]. The Medical Gas Data Sheet for 5%CO_2: 95%O_2 states that 5%CO_2: 95%O_2 is "not contraindicated in pregnancy" [37].

If it is discovered that the participant was pregnant at the time of treatment, this should be reported to the LCTC using a pregnancy CRF within 24 hours of awareness and the pregnancy followed up until after the outcome using the pregnancy CRF.

Any pregnancies which result in a safety event assessed as "serious" (e.g. birth defect) must also be reported separately on the appropriate Safety Event CRFs in accordance with processes described in section 11.11. All pregnancies and outcomes reported to LCTC will be notified to the study Sponsor and monitored by trial oversight committees.

11.9 Reporting of Overdose

For reasons discussed in section 8.9 overdose is not possible in this study.

11.10 Reporting of Death

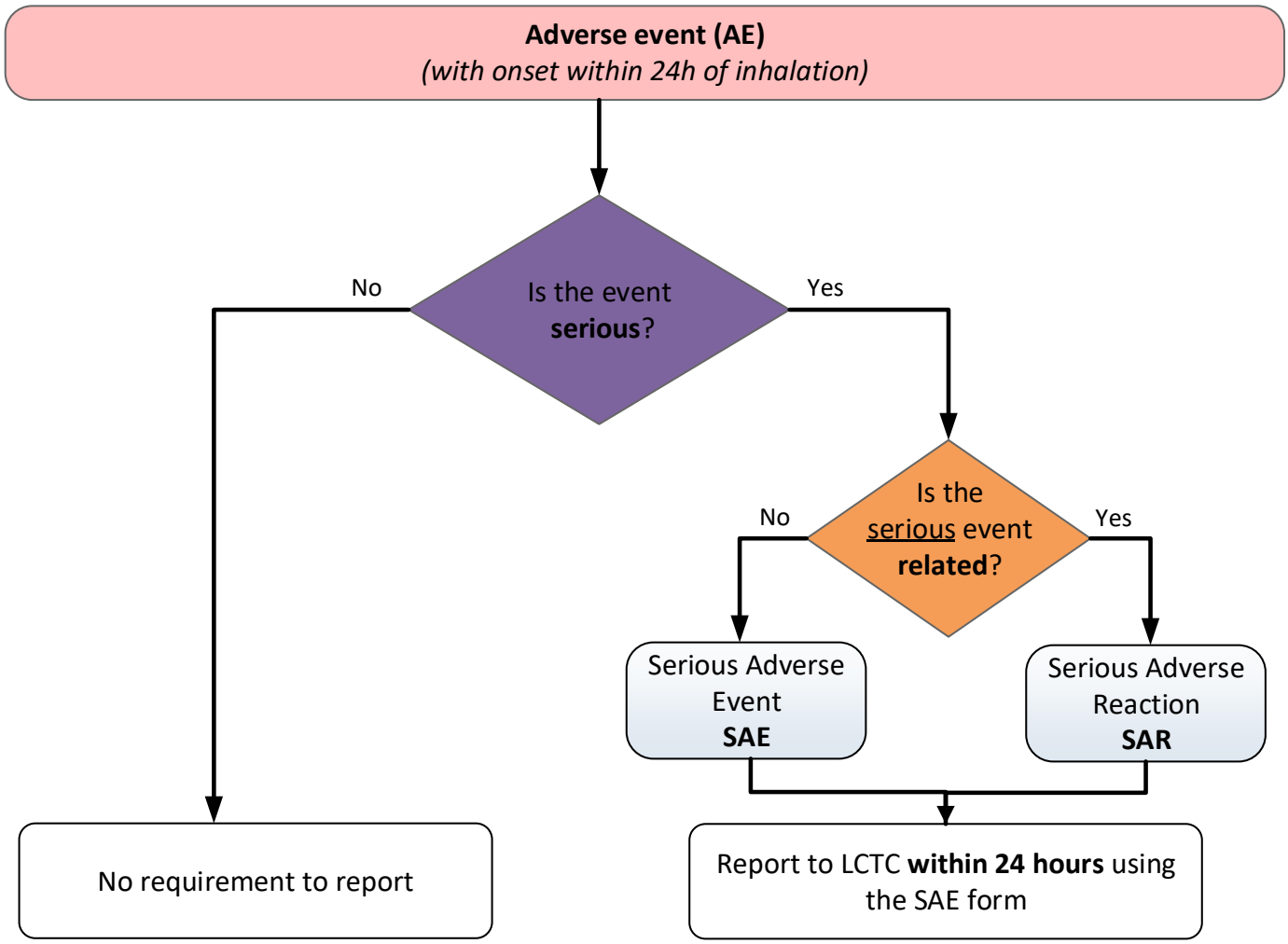
Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE CRF. Generally, only one such event should be reported. The term **"sudden unexpected death in epilepsy (SUDEP)"** [56, 57] should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac effects of a seizure in a patient with known epilepsy. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the SAE CRF. If the cause of death subsequently becomes available (e.g. after autopsy), "unexplained death" should be replaced by the established cause of death.

All deaths that occur within 30 days after randomisation should be reported on a Serious Adverse Event CRF and emailed to LCTC within 24 hours.

11.11 Reporting Procedures

All serious safety events and reactions which are recorded for the study should be reported following the procedures detailed below. The occurrence of a safety event may come to the attention of research staff from the participant's notes, directly from the participant or by other means. Note that reporting procedures vary dependent on the nature of the incident (i.e. "serious" events are to be reported to LCTC in an expedited manner). Any questions concerning adverse event reporting should be directed to the LCTC in the first instance. A flowchart is given below to aid in determining reporting procedures for different types of adverse events. Any questions concerning serious adverse event reporting should be directed to the LCTC in the first instance.

Safety reporting flow chart



Safety events which are assessed as "serious" must be recorded on Serious Adverse Event (SAE) Forms; a single form is used for each individual event (i.e. a single diagnosis), though multiple symptoms can be recorded. Where additional information is received by site after initial submission to LCTC, this should be provided on a follow-up form within 5 days. However, if this information changes the causality or seriousness then this should reported within 24 hours. SAE Forms collect data regarding the nature of event, date of onset, severity, corrective therapies given, outcome and causality; all serious events reported to LCTC will be reviewed by the Chief Investigator or Medical Reviewer, and assessed for causality and expectedness.

Follow-up After Adverse Events

All reportable adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable. When reporting “serious” safety events the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes:

- resolved
- resolved with sequelae (specifying with additional narrative)
- not resolved/ongoing
- ongoing at final follow-up
- fatal or unknown.

11.12 Investigator Responsibilities

The PI is responsible for ensuring that all safety events requiring recording on this study (see section 11.2) which the local research team becomes aware of are reported to LCTC. It is the responsibility of the PI or delegate as recorded on the Delegation Log (medically qualified person) to assess the seriousness and causality of events. When documenting any adverse events the correct medical terminology must be used in accordance with MedDRA.

Safety events which meet the definition of “serious” must be reported to the LCTC Central Safety Team (lctcsafe@liverpool.ac.uk) on an SAE form and reported **immediately and in no circumstances later than 24 hours from becoming aware** where they will be appropriately processed.

The SAE form should be completed by an appropriately delegated member of the research team; the assessments of seriousness and causality must be performed by an appropriately medically qualified person. Minimum reporting information must be provided in initial reports for all studies.

Minimum information required for reporting:

Minimum information required from site	Corresponding data / information
Valid registration number (EudraCT / ISRCTN) and Sponsor study number	**Pre-populated in header:** EudraCT/ISRCTN number and sponsor study number
One identifiable coded subject	Patient study number
One identifiable reporter	Study site number
	Reporting site research team member (PI/delegate)
One serious safety event	Description of the event, including date of onset
	The reason why the event is classified as serious
One suspect IMP	Suspect IMP (including active substance name- code)
A causality assessment	Investigator assessment of causality

N.B. In the absence of a delegated medically qualified person the form should be completed and signed by an alternative member of the research site trial team and submitted to the LCTC. As soon as possible thereafter the responsible investigator should check the SAE form, make amendments as appropriate, sign and re-send to the LCTC. The initial report shall be followed by detailed follow-up reports as appropriate.

Safety events should be reported to the site R&D team in accordance with local policy.

11.13 LCTC Responsibilities

The trial Sponsor, The Newcastle upon Tyne Hospitals NHS Foundation Trust, has delegated to LCTC the duty of onward reporting of safety events to REC, MHRA and Sponsor. SOPs will be followed to ensure appropriate reporting as detailed below.

All “serious” safety events will be forwarded to the Chief Investigator or Medical Reviewer by LCTC within 24 hours of receiving the minimum information from site. The CI (or delegate) will review information provided by site and for all events assessed as “related” will provide an assessment of “expectedness”.

Safety events which are assessed as “serious”, “related” and “unexpected” will be expedited to REC and MHRA as a SUSAR within the following timeframes:

- SUSARs which are fatal or life-threatening – **as soon as possible and in any case no later than 7 days** after the LCTC is first aware of the event. If the initial report is incomplete, a complete report will be submitted within an additional 8 days.
- SUSARs that are not fatal or life-threatening – **within 15 days** of the LCTC first becoming aware of the event.

Additionally, SUSARs will be reported to the trial Sponsor and Principal Investigators of participating sites within the agreed timelines.

The LCTC will submit an Annual Safety Report to REC and a Development Safety Update Report to the MHRA on an annual basis.

The PIs at all institutions participating in the trial will be notified of any SUSARs within a reasonable timeline, and if appropriate, accompanied by a summary of the evolving safety profile of the IMP.

Any concerns raised by the TSC and IDSMC or inconsistencies regarding safety reporting noted at a given site may prompt additional training at sites, with the potential for the LCTC to carry out site visits if there is suspicion of unreported SAEs/SARs in patient case notes. Additional training will also be provided if there are unacceptable delays in safety reporting timelines.

Maintenance of Blinding in Adverse Event Reporting

Systems for reporting safety events assessed as “related” (e.g. SAR and SUSAR) should, as far as possible, maintain blinding of individual clinicians and of trial staff involved in the day-to-day running of the trial. SAE forms allow reporting investigators to make an assessment of causality without having to unblind the participant. Emergency (contemporaneous) unblinding will not be available (see section 8.10). Cases that are considered serious, unexpected and related to the intervention (i.e. SUSARs) will have to be unblinded at LCTC prior to onward reporting.

All Suspected Unexpected Serious Adverse Reactions (SUSARs) must be reported unblinded. For SUSAR reporting, the LCTC Central Safety Team will contact the randomising statistician for the treatment allocation.

Safety Reports

Safety reports will be generated during the course of the trial which allows for monitoring of safety events including reporting rates and safety events by site and arm. The LCTC will send annual developmental safety update reports (DSURs) and Annual Progress Reports (APRs) containing a list of all SAEs and SARs to the IDSMC, MHRA and the main REC. If any safety reports identify issues that have implications for the safety of trial participants, the PIs at all institutions participating in the trial will be notified.

Urgent Safety Measures (USMs)

An urgent safety measure (USM) is a procedure to protect clinical trial participants from any immediate hazard to their health and safety but has not previously been defined by the protocol. It can be put in place prior to authorisation by the REC and the MHRA.

The LCTC will notify the MHRA and REC immediately and, in any event, within 3 days that such a measure has been taken and the reasons why it has been taken. The initial notification to the REC and MHRA will be by telephone (ideally within 24 hours) and a notice in writing will be sent within 3 days, setting out the reasons for the USM and the plan for further action. After discussion with the REC and MHRA, further action will be agreed, which may include submission of a substantial amendment, a temporary halt, or permanent termination of the trial.

Following notification, if a substantial amendment is required this must be submitted as soon as possible to the REC and ideally within two weeks to the MHRA. If the study is temporarily halted it may not recommence until authorised to do so by the REC and MHRA. If the study is permanently terminated before the date specified for its conclusion (in the original applications to REC and MHRA), the Sponsor should notify the REC and MHRA within 15 days of the date of termination by submitting the formal End of Trial Notification.

11.14 Contact Details and Out-of-hours Medical Cover

CRESCENT is being conducted within EDs of sites with expertise in the management of paediatric emergencies. The perturbation of acid-base status due to 5%CO_2: 95%O_2 inhalation is transient (and almost certainly of lesser magnitude than that due to the CSE itself: see section 5.3) with no foreseeable ongoing consequences. Emergency unblinding is not required (section 8.10): knowing that a child has had an episode of CSE, has received standard APLS treatment and was inhaling either 100% O2 or 5%CO_2: 95%O_2 is sufficient data to enable physicians to make appropriate and informed decisions about ongoing care in the event of an emergency. As such, emergency clinical care out of hours will be provided as local standard of care.

During office hours, the CI or delegate are able to provide medical advice in relation to participation using the contact details listed at the beginning of this document.

12 STATISTICAL CONSIDERATIONS

12.1 Sample Size

In EcLiPSE, of 1432 screenings, 286 went on to receive second-line treatment as part of EcLiPSE suggesting an 80% success rate of first-line intervention [8]. However, screening practices varied at sites with some sites only entering participants on to screening logs once progression to second-line intervention became increasingly likely. Restricting to those sites where screening data included all children presenting with a seizure a success rate of 85% was observed for first line treatment.

Using a control group success rate for first-line treatment of 85% we aim to detect a 10% increase using a group sequential design with one interim analysis planned following observation of the primary outcome for 50% of the recruitment target. Sample size calculations are undertaken in NQuery using the O'Brien-Fleming spending function used to determine the upper efficacy test boundary (0.025) and the futility boundary (non-binding).

Bounds for efficacy to reject the null hypothesis are 2.963 and 1.97 respectively for the interim and final analysis with the futility boundary for acceptance of the null hypothesis at the interim analysis being 0.254. This requires 191 participants per group for the final analysis to achieve 5% two-sided Type 1 and 10% Type II error rates.

As with EcLiPSE data completeness is expected to be exceptionally high (99%), however the overall sample size target is inflated to allow for a maximum of 10% loss to follow up.

Stop/Go Criteria

The trial will include a 12-month internal pilot with stop/go criteria. Sites open and recruiting for a minimum of 3 months each will be included.

Stop/go criteria are based upon Recruitment, Consent Rate and Data Completeness criteria:

(A) Recruitment.

If the recruitment data support trial delivery within the specified 24 months, proceed to main trial. If it is predicted that the recruitment period will need to be extended by 12 months or less consider and introduce ways to reduce this. If it is predicted that recruitment will need to be extended beyond an additional 12 months, with no obvious mitigating solutions, abandon the plan for the full trial.

(B) Deferred consent.

If the deferred consent rate is 90% or more, proceed to main trial. If deferred consent rate is between 70% and 90%, and there is no clear association between provision of deferred consent and the child's outcome, then analyse reasons why patients/guardians do not want to participate to identify any aspects amenable to change. Then proceed to main trial as amended. If deferred consent is less than 70%, and/or consent refusal is associated with patient outcome consider abandoning the main trial.

(C) Completeness of primary outcome data.

If primary outcome data are available for over 95% of randomised and consented participants, proceed to main trial. If primary outcome data are available for 70–95% of randomised and consented participants, analyse reasons for missing data and identify whether any aspects are amenable to change. Then proceed to main trial as amended. If primary outcome data are available for less than 70% of participants randomised and consented abandon the plan for the main trial.

12.2 Method of Randomisation

12.2.1 **Allocation Sequence Generation**

A computer-generated random allocation sequence will be generated by LCTC and supplied to BOC at study opening to inform the sequence of cylinder content fillings (1:1 ratio). Cylinders are used in numbered sequence order.

12.3 Interim Analyses

CRESCENT is a group sequential design with one interim analysis planned following observation of the primary outcome for 50% of the recruitment target. The boundaries for the interim analysis are described within the sample size calculation section 12.1.

The timing of interim analyses may be altered at the discretion of the IDSMC. The results of this and any other interim analyses will be reviewed by the IDSMC who will make recommendations to the Trial Steering Committee regarding trial continuation and modification. A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community.

12.4 Analysis Plan

A full statistical analysis plan (SAP) will be written prior to the conduct of any comparative analysis of the treatment arms.

The primary analysis will use the intention to treat principle. A 5% level of statistical significance will be used throughout and all results will be presented with 95% confidence intervals (95% confidence interval for the primary outcome calculated to allow for interim analysis alpha-spend). A detailed statistical analysis plan will be written prior to the first meeting of the IDSMC in which unblinded data are required.

The primary outcome is success of first-line treatment of CSE (i.e. child did not need to receive second-line or rescue therapy as defined within the APLS guidelines or their personal treatment plan). Success of first line treatment is defined as not requiring intravenous phenytoin, phenobarbital, valproate, levetiracetam or RSI. The emergency nature of the project limits the potential to stratify the randomisation process. Instead the primary analysis will be by logistic regression and will include known prespecified important prognostic indicators (weight, age). The primary outcome will be analysed using logistic regression and will adjust for these prespecified variables.

Binary outcomes will be analysed as per the primary outcome.

Two prespecified, exploratory analyses will be conducted. We will examine whether there is evidence of greater response rates to carbogen:

1) In children whose first blood pH is more alkalotic (i.e. evidence of an interaction between membership of the active treatment arm and admission blood pH in determining the primary outcome)

2) In children deemed to have had a febrile CSE episode (i.e. evidence of an interaction between membership of the active treatment arm and whether the CSE was deemed of febrile aetiology in determining the primary outcome)

As much information as possible will be collected about the reasons for missing outcome data; this will be used to inform any imputation approaches employed in the analysis. Such methods will be fully described in the SAP.

13 DATA MANAGEMENT AND TRIAL MONITORING

For the CRESCENT trial the responsibilities for Data Management and monitoring are delegated to the LCTC. Separate Data Management and Trial Monitoring Plans have been developed which provide detail regarding the internal processes that will be conducted at the LCTC throughout the trial. Justification for the level of monitoring is provided within those documents and the trial-specific risk assessment. All data will be managed as per LCTC processes and in line with all relevant regulatory, ethical and legal obligations.

13.1 Source Documents

The case report form (CRF) will be considered the source document for data where no prior record exists and which is recorded directly in the bespoke CRF. A CRESCENT source document list will be produced for each site to be kept in the ISF and provide detail of what constitutes CRESCENT-specific source data.

Date(s) of informed consent and assent processes (including date of provision of patient information, randomisation number and the fact that the patient is participating in a clinical trial (including possible treatment arms) should be added to the patient's medical record chronologically.

13.2 Data Collection Methods

Participant CRF folders will be provided to sites for local completion by members of the research team trained and delegated the duty. Trial staff named at each site will enter data from source documents corresponding to a participant's visit onto the relevant CRF in the participant's folder. The CRF is the primary data collection instrument for the study so all data requested on the CRF **must** be recorded and all missing data must be explained. A copy of all CRFs should be retained at site. Any corrections should be made in accordance with GCP.

13.3 Monitoring

Monitoring is conducted to ensure protection of patients participating in the trial and all aspects of the trial (procedures, laboratory, trial intervention administration and data collection) are of high quality and conducted in accordance with sponsor and regulatory requirements.

A detailed Trial Monitoring Plan will be developed and agreed by the TMG, Sponsor and CI to describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted. This will be dependent on the documented risk assessment of the trial which determines the level and type of monitoring required for specific hazards. All processes may be subject to monitoring, e.g. enrolment, consent, adherence to trial interventions, accuracy and timeliness of data collection etc.

Trial Oversight Committees related to the monitoring of the trial are detailed in Roles and Responsibilities see section 4.

Central Monitoring

There are a number of monitoring features in place at LCTC to ensure reliability and validity of the trial data, to be detailed in the trial monitoring plan. Data will be entered into a validated database and during data processing there will be checks for missing or unusual values (range checks) and for consistency within participants over time. Other data checks relevant to patient rights and safety will also be regularly performed as per LCTC processes. Any suspect data will be returned to the site in the form of data queries. Data query forms will be produced at LCTC from the trial database and sent either electronically or through the post to a named individual (as listed on the site delegation log). Sites will respond to the queries providing an explanation/resolution to the discrepancies and return the data query forms to LCTC. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database.

Site monitoring visits may be 'triggered' in response to concerns regarding study conduct, participant recruitment, outlier data or other factors as appropriate.

Clinical Site Monitoring

In order to perform their role effectively, the trial manager and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g. patient medical records, laboratory reports, appointment books, etc. Since this affects the participant's confidentiality, this fact is included on the PISC. In agreeing to participate in this study, a PI grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation. The purposes of site monitoring visits include, but are not limited to:

- assessing compliance with the study protocol;
- discussing any emerging problems that may have been identified prior to the visit;
- checking CRF and query completion practices.

13.4 Risk Assessment

A full and comprehensive risk assessment has been conducted for CRESCENT with a monitoring plan developed appropriate to risks identified.

13.5 Confidentiality

Where consent is not obtained for a participant, data provided to the LCTC is considered fully anonymous. Where consent is obtained, data is considered identifiable (i.e. Personal Data under data protection legislation) – the consent process obtains permissions for disclosure under Common Law Duty of Confidentiality purposes. Where possible, pseudonymisation will be applied at LCTC.

All data collected on this trial, whether anonymous, pseudonymous or directly identifiable, will be handled and processed confidentially and securely and in accordance with applicable data protection legislation.

Data (including special category) will only be collected, used and stored if necessary for the trial (e.g. evidencing provision of consent, for data management and central monitoring, statistical analysis, regulatory reporting, etc.).

CRFs will be labelled with a unique trial randomisation number. CRFs received at LCTC will contain non-identifiable data and will be considered anonymous until the corresponding consent/assent form is received. Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent and assent forms being supplied to LCTC by recruiting sites. This transfer of identifiable data is disclosed in the PISC.

N.B. Consent forms must be transferred separately to any other trial documentation to ensure the pseudonymisation of special category data is maintained.

Site-specific study-related information will be stored securely and confidentially at sites and all local relevant data protection policies will be adhered to.

The LCTC as part of The University of Liverpool will preserve the confidentiality of participants taking part in the study. The University of Liverpool and The Newcastle upon Tyne Hospitals NHS Foundation Trust are registered as Data Controllers with the Information Commissioners Office.

Breaches of data protection principles or regulations identified by LCTC will be notified promptly to the trial Sponsor and The University of Liverpool's Data Protection Officer and appropriate processes followed.

13.6 Quality Assurance and Control

To assure protocol compliance, ethical standards, regulatory compliance and data quality, as a minimum, the following will occur:

- The PI and other key staff from each site will attend initiation training, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol.
- The TMG will determine the minimum key staff required to be recorded on the delegation log in order for the site to be eligible to be initiated.
- The TC at the LCTC will verify appropriate approvals are in place prior to initiation of a site and the relevant personnel have attended the trial specific training. A greenlight checklist will verify all approvals are in place prior to trial initiation at LCTC and the individual site.
- The trial will be conducted in accordance with procedures identified in the protocol.
- The IDSMC and independent members of the TSC will provide independent oversight of the trial.
- The TMG will monitor screening, randomisation and consent rates between sites and compliance with the protocol.
- Data quality checks and monitoring procedures will be undertaken in line with the trial Data Management Plan and Monitoring Plan.

13.7 Records Retention

The retention period for the CRESCENT data and information is 25 years from the official End of Trial date (defined in section 10.11 above).

The PI at each investigational site must make arrangements to store the essential trial documents (as defined by ICH GCP guidelines) including the Investigator Site File, the applicable participant

medical records and Pharmacy Site File, for the full length of the trial's retention period and will arrange for confidential destruction at the end of this period as instructed by the Sponsor via the LCTC.

The PI is also responsible for archiving all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities). They must ensure the continued storage of the documents, even if they, for example, leave the clinic/practice or retire before the end of required storage period. Delegation of responsibility for this must be documented in writing.

All other persons and organisations involved in the trial will be responsible for storing and archiving the parts of the TMF relevant to their delegated duties (i.e. IMP manufacturer/distributor).

The LCTC undertakes to archive as per their contractual requirements; documents will be archived in compliance with the principles of GCP. All electronic CRFs and trial data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to secure premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

14 REGULATORY AND ETHICAL CONSIDERATIONS

14.1 Statement of Compliance

The trial will be administered in line with The Medicines for Human Use (Clinical Trials) Regulations 2004 (and amendments) and principles of Good Clinical Practice. The trial will also comply to LCTC SOPs.

14.2 Ethical Considerations

The trial will adhere to the principles of the World Medical Association Declaration of Helsinki and has been designed to be as pragmatic as possible. The protocol has undergone ethical review by an independent Research Ethics Committee and has received a favourable opinion.

The specific ethical issues are:

A. Informed consent in a paediatric emergency care setting

Prospective informed consent cannot be sought for CRESCENT as:

- seizures are a medical emergency and there is insufficient time to obtain informed consent within the therapeutic window (oxygen is provided within tens of seconds of hospital admission);
- staff priorities are assessment and management of airway, breathing, circulation with establishment of IV access and brief pertinent clinical history;
- parents may not be present; and even when parents are present seizures are very distressing, compromising parents' capacity to make an informed decision and provide consent.

In 2008, the UK amended its regulations to allow deferred consent in paediatric emergency trials that fulfil specific criteria. This trial will comply with these regulations as the emergency need for immediate treatment will not allow informed consent prior to randomisation. Deferred consent will be sought as soon as is practicably possible (within 24 hours).

B. Assent from critically ill patients (minors)

Due to the physical status of the target population it may not be possible to involve children in the consenting process. Deferred assent of older children and young people will be obtained if their condition allows.

C. Recruitment of adults lacking capacity (over 16 years old)

Due to the physical status of the target population it may not be possible to involve eligible adults in the consenting process. The adult participants (16-18 years) are likely to have severe and drug-resistant epilepsy and additional co-morbid problems, including moderate or severe learning difficulties and autistic spectrum disorder and therefore may not have the capacity to give informed consent outside of the acute emergency setting. It is likely that less than 2% of all participants will be aged between 16 and 18 years.

CRESCENT fulfils the criteria set out in UK law to allow adults not able to consent for themselves to be recruited into Clinical Trials of Investigational Medicinal Products (CTIMPs) without prior consent in emergency situations. In these situations, deferred consent from the trial participant will be sought should they have capacity to do so. However, for adults lacking capacity a legal representative will be sought. The legal representative will be asked to provide consent on behalf of an adult lacking capacity to provide consent themselves. The informed consent given by the legal representative shall represent the presumed will of the incapacitated adult.

If it is appropriate the participants themselves will also receive information, according to their capacity of understanding, about the trial and its risks and benefits.

14.3 Approvals

The protocol, patient/guardian information, consent and assent material will be submitted to an appropriate Research Ethics Committee (REC), MHRA, Health Research Authority (HRA) and host institution(s) for written approval.

Any substantial amendments to the original approved documents will be submitted and, where necessary, approved by the above parties before use.

14.4 Protocol Deviation and Serious Breaches

Deviations from, breaches or violations of, or non-compliance to either the protocol, the conditions or principles of GCP, and MHRA and REC requirements are handled based on their nature and severity.

Non-Serious breaches

Protocol deviations and other non-serious breaches of GCP etc. will be managed according to local site and LCTC procedures as appropriate. They will be reported to trial oversight committees.

Serious breaches

A breach of the protocol or GCP is ‘serious’ if it meets the definition of being “likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the trial”. This assessment can only be determined by the Sponsor.

If any persons involved in the conduct of the trial become aware of a potential serious breach, they must immediately report this to the LCTC who will in turn notify the Sponsor. The Sponsor will assess the breach and determine if it meets the criteria of a ‘serious’ breach.

The Sponsor may seek advice from medical expert members of the TMG and/or of the independent oversight committees (IDSMC and TSC) in determining whether or not the breach is likely to affect to a significant degree the safety, physical or mental integrity of participants.

The Sponsor may seek advice from the Trial Statistician in determining whether or not the breach is likely to significantly affect the scientific value of the trial. However, the Sponsor retains responsibility for the assessment of whether or not a breach meets the definition of ‘serious’ and is subject to expedited reporting to MHRA and REC.

Breaches confirmed as ‘serious’ will be reported to MHRA and REC within 7 days by LCTC on behalf of the Sponsor and notified to the TMG, IDSMC and TSC at their next meeting.

Any requests for additional information from the Sponsor, TMG, TSC, IDSMC, MHRA or REC, will be promptly actioned by the relevant member(s) of the research team and open communication will be maintained to ensure appropriate corrective actions are taken and documented.

Incidents of protocol non-compliance will be recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

15 INDEMNITY

The Newcastle upon Tyne Hospitals NHS Foundation Trust has liability for clinical negligence. NHS indemnity for clinical trials conducted with NHS permission will apply for clinical negligence that harms individuals towards whom the NHS has a duty of care. This is a non-commercial trial and therefore there is no provision for indemnity in respect of non-negligent harm.

Indemnity in respect of potential liability arising from negligent harm related to trial design is provided by Newcastle University as the CI's substantive employer.

The trial sites will provide indemnity in the event that trial participants suffer negligent harm due to the conduct of the trial at their site. This indemnity will be provided under the NHS indemnity arrangements for clinical negligence claims in the NHS. NHS Organisations must ensure that site staff without substantive NHS contracts hold honorary contracts to ensure they can access patients and are covered under the NHS indemnity arrangements.

16 PUBLICATION AND DISSEMINATION

16.1 Publication Policy

The results from different participating sites will be analysed together and published as soon as possible, maintaining participant confidentiality at all times. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group (TMG).

The TMG will form the basis of the writing committee and will advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants and if there are named authors these should include the trial's Chief Investigator(s), Statistician(s) and Trial Manager(s) involved as a minimum. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial will be attached to any publications resulting from this trial and members of the TSC and IDSMC should be acknowledged.

Any publications arising from this research will be reviewed appropriately prior to publication.

Authorship

Contributors to all four of (i) the design, conduct, data analysis and interpretation, (ii) writing, (iii) manuscript approval and (iv) accountability for the integrity of the work will, depending on their contribution and journal requirements, be included by name at the manuscript head or listed at the end in a by-line as members of the CRESCENT Consortium and PERUKI which will also be named at the manuscript head.

16.2 Dissemination to Key Stakeholders

On completion of the research, a Final Trial Report will be prepared and submitted to the Funder, MHRA and REC. The results of CRESCENT will be published regardless of the magnitude or direction of effect.

16.3 Data Sharing

At the end of the trial, after the primary results have been published, the anonymised individual participant data and associated documentation (e.g. protocol, annotated blank CRF) will be prepared in order to be shared with external researchers. All requests for access to the trial data will be discussed with the Sponsor in accordance with the Sponsor policy on data sharing.

17 CHRONOLOGY OF PROTOCOL AMENDMENTS

17.1 Version 2.0 (12/JUL/2022)

Summary of Amendments from Protocol V1.0 to Protocol V2.0		
Protocol Section Number	**Protocol Section Title**	**Summary of Changes**
Front Page	N/A	Addition of reference numbers for Research Ethics and CTA
Protocol Approval Page	Protocol Approval	Name of Sponsor representative updated.
8.1	Introduction	Correction to medical gas cylinder capacity
10.7.4	Information Sheets, and Deferred Consent and Assent Forms	Wording added to confirm that the study results will be translated into the languages spoken by those participants who do not speak English.
10.7.5	Definitions of Legal Representatives	Wording added to clarify that a professional legal representative must not be the PI or a member of the study team.
10.7.6	Death Prior to Deferred Consent being sought	Removal of reference to a follow-up letter.
10.7.7	Discharge/Transfer Prior to Deferred Consent being sought	Wording added to clarify that if after three attempts it has not been possible to contact a participant/parent/legal representative, the PISC and accompanying letter can be sent to the participant/parent/legal representative.
10.7.8	Action in event of lack of response to written approaches for consent with reminders	Wording added to clarify that for bereaved families if a response as not been received after 8 weeks of the letter then no personal identifiable data will be sent to the LCTC.

17.2 Version 1.0 (04/APR/2022)

Original version was not approved. Amendments were requested by REC and HRA.

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19 DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL

Documents referenced within the protocol are separately maintained and version controlled. Any of the supplementary documents subject to CA and/or Ethical review are submitted as separate version-controlled documents.