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Carbogen for status epilepticus in children trial

Submission date 07/05/2022	**Recruitment status** Recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 27/07/2022	**Overall study status** Ongoing	
Last Edited 30/12/2025	**Condition category** Nervous System Diseases	

Plain English summary of protocol

Background and study aims
An epileptic seizure that is not stopping is a medical emergency. The longer it lasts the greater the risk of brain damage or even, occasionally, death. We need better ways to stop long seizures sooner. We believe creating a slightly more acidic environment within the brain may help this. One convenient and safe way to alter brain acidity is to give someone a different gas mixture to breathe. Our bodies take oxygen out of the air we breathe in; we then breathe out carbon dioxide as a “waste” gas. Carbon dioxide is very slightly acidic: if you mix a small amount (5%) with oxygen it makes the body and brain slightly acidic. This mixture is called Carbogen. It still has much more oxygen in it than room air (95% compared to 21%), and only the same amount of carbon dioxide as in the air we normally breathe out.

Who can participate?
Children with ongoing seizures.

What does the study involve?
Half the children will receive standard drug treatment whilst breathing 100% oxygen (which is what happens currently) and the other half will receive standard drug treatment whilst inhaling Carbogen. The choice of whether a child is given Oxygen or Carbogen will be random. All children will receive the same standard medical drug treatment for their seizure.
Because this is an emergency situation, there isn’t time to give children's families information about the trial or ask if they wish to take part before the treatment is given. Families will be told that their child was in the trial and will be asked for their consent to remain in the study. This is known as “deferred consent”. We have recently successfully completed a trial of another treatment of ongoing seizures this way and found families understood and accepted this.

What are the possible benefits and risks of participating?
Benefits:
As most medicines used in the treatment of Chronic Status Epilepticus (CSE) have sedating (induces a state of calm or sleep) or anaesthetic (reduces sensitivity to pain) properties, breathing complications are common. In contrast, Carbogen is non-sedating, and may actually act to stimulate breathing. The effects of Carbogen are potentially both rapidly acting and rapidly reversible. Whilst there has been no long-term benefit currently observed in the use of Carbogen in preventing seizures from occurring in the future, use of Carbogen during an ongoing seizure may help to stop the seizure quicker.

Risks:
The direct burden of participation will be minimal. The experience of the trial intervention is identical to standard care (inhaling a medical gas via facemask alongside standard medical care). Since by definition children are in an ongoing seizure their awareness of involvement will be very limited if any. There are no additional visits, blood tests or other investigations arising from trial participation beyond standard care: all follow-up is based on data extraction from hospital notes.
Inhalation of much higher proportions of carbon dioxide in air than are being used here (20-30%) in awake volunteers causes a distressing sense of panic and “air hunger” that rapidly and immediately ends upon discontinuation. However we and others have shown that inhalation of 5% carbon dioxide is well tolerated by awake children. Again because these children are in a seizure they are unlikely to have any subjective sense of breathlessness.
Increasing the proportion of carbon dioxide in inhaled air will cause very slight increases in blood flow and pressure in the brain: they are equivalent to those that occur if someone holds their breath, which causes carbon dioxide levels in the blood to rise by similar amounts. They are dwarfed by the effects on blood flow and pressure of the seizure itself.
There are two conditions that in an emergency setting are sometimes mistaken for and treated as prolonged epileptic seizures: these are (i) non-epileptic attack disorder (NEAD) where someone erroneously believes they are having a seizure and imitates its features, sometimes as a result of emotional or psychological distress and (ii) a rare situation where critically ill unconscious patients can exhibit unusual sustained stiff postures.
Treating the NEAD group for epileptic seizures is not inherently dangerous but exposes patients to medications and procedures unnecessarily and potentially entrenches an erroneous diagnosis of epilepsy. Treating the second group for epileptic seizures can be harmful because in general causing further sedation and depressing breathing effort (which is a common side effect of medications for epilepsy) can make this situation worse. We have carefully considered any possible additional risk to patients in this second group from receiving carbogen (i.e. any additional risk from being in the active rather than the treatment-as-usual arm of the trial) and believe these are acceptable. However we have incorporated specific training for participating sites to make them aware of these two conditions and to improve diagnostic assessment skills in this difficult, emergency situation. Generally this second condition is not hard to suspect or diagnosis: the issue is awareness of the existence of the phenomenon. By offering specific site training we will be improving care for this rare clinical situation generally.
For parents there may be some anxiety resulting from the deferred consent model and the retrospective discovery of their child's participation in a trial where they may have received a novel therapy. However, experience from our previous trial (ECLIPSE), suggests this is not a major issue particularly where treatment has clearly been successful and the seizure terminated. In ECLIPSE, one of 286 children enrolled died due to complications of convulsive status epilepticus. We have had PPI help in preparing specific material informing the family of a child who has died about the trial.

Where is the study run from?
Liverpool Clinical Trials Centre (UK)

When is the study starting and how long is it expected to run for?
October 2021 to January 2027

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK)

Who is the main contact?
CRESCENT Trial Team, crescent-trial@liverpool.ac.uk

Contact information

Type(s)
Scientific

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Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2021-005367-49

Integrated Research Application System (IRAS)
1004295

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
R&D09684/NU00021, CPMS 52343

Study information

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

Acronym
CRESCENT

Study objectives
The main research objectives are 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.

Exploratory objectives are:
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.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 19/07/2022, North West - Liverpool Central Research Ethics Committee (3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0)207 1048118, +44 (0)207 1048222, +44 (0)207 1048016; liverpoolcentral.rec@hra.nhs.uk), Ref: 22/NW/0162

Study design
Interventional double-blind randomized controlled trial

Primary study design

Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Severe epileptic seizures in children that are not stopping by themselves and require emergency medication to stop them

Interventions
Carbogen Arm (Intervention)
Drug Name/Active Ingredient: Carbogen®; 5% CO_2: 95% O_2
Formulation: Medical Gas
Dose: 150 Litres
Dose Frequency: Once
Route of Administration: Oral Inhalation via standard hospital issued non-rebreather mask.
Duration of Treatment: 10 minutes
Strength: 15 Litres/minute
Follow-up Activity: Follow-up Activity: No follow-up intervention. Primary and secondary outcomes are measured in real-time during intervention and at 24-hours and 30-days post-randomisation. The primary outcome measure will be measured as the success of first-line treatment of Chronic Status Epilepticus, defined as the participant not requiring intravenous phenytoin, phenobarbital, valproate, levetiracetam or Rapid Sequence Induction within the same epileptic episode. Seizure activity visible at 5 minutes and 15 minutes post-commencement of inhalation will be recorded as an outcome measure in real-time during intervention. The following outcomes are measured at 24-hours: was the participant admitted to critical care or a high dependency unit; seizure recurrence within 24-hours. 30-day mortality will be recorded as an outcome measure with serious adverse events and reactions recorded from randomisation up to 30-days post-randomisation, with an onset within 24-hours of intervention.

Oxygen Arm (Control)
Drug Name/Active Ingredient: 100% O_2
Formulation: Medical Gas
Dose: 150 Litres
Dose Frequency: Once
Route of Administration: Oral Inhalation via standard hospital issued non-rebreather mask.
Duration of Treatment: 10 minutes
Strength: 15 Litres/minute
Follow-up Activity: No follow-up intervention. Primary and secondary outcomes are measured in real-time during intervention and at 24-hours and 30-days post-randomisation. The primary outcome measure will be measured as the success of first-line treatment of Chronic Status Epilepticus, defined as the participant not requiring intravenous phenytoin, phenobarbital, valproate, levetiracetam or Rapid Sequence Induction within the same epileptic episode. Seizure activity visible at 5 minutes and 15 minutes post-commencement of inhalation will be recorded as an outcome measure in real-time during intervention. The following outcomes are measured at 24-hours: was the participant admitted to critical care or a high dependency unit; seizure recurrence within 24-hours. 30-day mortality will be recorded as an outcome measure with serious adverse events and reactions recorded from randomisation up to 30-days post-randomisation, with an onset within 24-hours of intervention.

Randomisation
The eligibility of potential participants will be assessed upon presentation to the Emergency Department. Portable medical gas cylinders containing either Carbogen or 100% Oxygen will be manufactured by British Oxygen Company Ltd (BOC Ltd). Treatment allocation is blinded to all trial staff and the participant. Each medical gas cylinder will be blinded for the medical gas contained within, and therefore, the treatment allocation. Medical gas cylinders will be labelled with an alphanumerical trial-specific identifier (CRESCENT Randomisation Number) which will be used to identify the participant throughout the trial and will also be used to indicate the order in which the medical gas cylinders should be utilised. For eligible participants, the trial researcher will retrieve the next available medical gas cylinder, in sequential CRESCENT Randomisation Number order, and initiate intervention immediately. The medical gas cylinders will be manufactured by BOC Ltd according to a specification (CRESCENT Randomisation List) provided by the Liverpool Clinical Trials Centre. The CRESCENT Randomisation List will dictate the medical gas content present within each medical gas cylinder, and therefore the treatment allocation, and the CRESCENT Randomisation Number associated to each medical gas cylinder. Each medical gas cylinder will only be used once and will be assigned to one participant only. No other formal randomisation tool will be used. Randomisation will be considered to have been performed at the point of intervention initiation.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Carbogen

Primary outcome(s)
Success of first-line treatment for presenting Chronic Status Epilepticus (CSE) (i.e. child did not need to receive second-line or rescue therapy as defined within the Acute Paediatric Life Support (APLS) guidelines or their personal treatment plan). Success of first line treatment for the presenting seizure is defined as not requiring intravenous phenytoin, phenobarbital, valproate, levetiracetam or Rapid Sequence Induction (RSI). Data for the 24hr period post-commencement of the intervention is captured on the Case Report Form (CRF) and completed following medical notes review.

Key secondary outcome(s))
1. Seizure activity visible at 5 minutes and 15 minutes post-commencement of inhalation captured on the Case Report Form (CRF).
2. Need for rapid sequence induction (RSI) with thiopentone or another agent (e.g. propofol) due to ongoing Chronic Status Epilepticus (CSE) observed in the 24-hours post-commencement of inhalation and captured on the CRF following medical notes review.
3. Need to be admitted to critical care (PICU) or high dependency unit observed in the 24-hours post-commencement of inhalation and captured on the CRF following medical notes review.
4. Seizure recurrence observed in the 24-hours post-commencement of inhalation and captured on the CRF following medical notes review.
5. Serious adverse events and reactions up to 30 days, with an onset within 24-hours of inhalation, captured on the CRF.
6. 30-day mortality post-randomisation captured on the CRF.

Completion date
30/01/2027

Eligibility

Key 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

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Sex
All

Total final enrolment
0

Key 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

Date of first enrolment
01/11/2022

Date of final enrolment
30/04/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
The Royal Victoria Infirmary and Associated Hospitals NHS Trust
Queen Victoria Road
Newcastle upon Tyne
England
NE1 4LP

Study participating centre
South Tyneside and Sunderland NHS Foundation Trust
Sunderland Royal Hospital
Kayll Road
Sunderland
England
SR4 7TP

Study participating centre
Bristol Royal Hospital for Children
Paul O'Gorman Building
Upper Maudlin Street
St Michael's Hill
Bristol
England
BS2 8BJ

Study participating centre
Alder Hey Children's Hospital
Eaton Road
West Derby
Liverpool
England
L12 2AP

Study participating centre
Royal Alexandra Children's Hospital
Eastern Road
Brighton
England
BN2 5BE

Study participating centre

Nottingham University Hospitals NHS Trust - Queen's Medical Centre Campus
Nottingham University Hospital
Derby Road
Nottingham
England
NG7 2UH

Study participating centre
Leeds General Infirmary
Great George Street
Leeds
England
LS1 3EX

Study participating centre
Barts Health NHS Trust
The Royal London Hospital
80 Newark Street
London
England
E1 2ES

Study participating centre
University Hospitals of Leicester NHS Trust
Leicester Royal Infirmary
Infirmary Square
Leicester
England
LE1 5WW

Study participating centre
University Hospitals of Derby and Burton NHS Foundation Trust
Royal Derby Hospital
Uttoxeter Road
Derby
England
DE22 3NE

Study participating centre
The Royal Wolverhampton NHS Trust
New Cross Hospital

Wolverhampton Road
Heath Town
Wolverhampton
England
WV10 0QP

Sponsor information

Organisation
The Newcastle upon Tyne Hospitals NHS Foundation Trust

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research Efficacy and Mechanism Evaluation Programme

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		29/05/2024	30/05/2024	Yes	No
HRA research summary			28/06/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes