

Carbogen for status epilepticus in children trial

Submission date 07/05/2022	Recruitment status Recruiting	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
Registration date 27/07/2022	Overall study status Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
Last Edited 09/09/2025	Condition category Nervous System Diseases	<input type="checkbox"/> Individual participant data <input checked="" type="checkbox"/> Record updated in last year

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 2026

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

Study website

<http://www.crescent-trial.org.uk/>

Contact information

Type(s)

Scientific

Contact name

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Type(s)

Principal Investigator

Contact name

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Type(s)

Public

Contact name

Dr CRESCENT Trial Team

Contact details

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Additional identifiers

EudraCT/CTIS number
2021-005367-49

IRAS number
1004295

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
R&D09684/NU00021, IRAS 1004295, 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

Secondary study design

Randomised controlled trial

Study setting(s)

Hospital

Study type(s)

Treatment

Participant information sheet

Not available in web format, please use contact details to request a participant information sheet

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% CO₂: 95% O₂

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% O₂

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 measure

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.

Secondary outcome measures

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.

Overall study start date

01/10/2021

Completion date

30/01/2026

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

Age group

Child

Sex

Both

Target number of participants

424

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

31/12/2025

Locations

Countries of recruitment

England

United Kingdom

Study participating centre

The Royal Victoria Infirmary and Associated Hospitals NHS Trust

Queen Victoria Road

Newcastle upon Tyne

United Kingdom

NE1 4LP

Study participating centre

South Tyneside and Sunderland NHS Foundation Trust

Sunderland Royal Hospital

Kayll Road

Sunderland

United Kingdom

SR4 7TP

Study participating centre

Bristol Royal Hospital for Children

Paul O'Gorman Building

Upper Maudlin Street

St Michael's Hill

Bristol

United Kingdom

BS2 8BJ

Study participating centre

Birmingham Women's and Children's NHS Foundation Trust

Steelhouse Lane

Birmingham

United Kingdom

B4 6NH

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

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

Study participating centre
Nottingham University Hospitals NHS Trust - Queen's Medical Centre Campus
Nottingham University Hospital
Derby Road
Nottingham
United Kingdom
NG7 2UH

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

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

Study participating centre

University Hospitals of Leicester NHS Trust

Leicester Royal Infirmary
Infirmary Square
Leicester
United Kingdom
LE1 5WW

Study participating centre**University Hospitals of Derby and Burton NHS Foundation Trust**

Royal Derby Hospital
Uttoxeter Road
Derby
United Kingdom
DE22 3NE

Study participating centre**The Royal Wolverhampton NHS Trust**

New Cross Hospital
Wolverhampton Road
Heath Town
Wolverhampton
United Kingdom
WV10 0QP

Sponsor information

Organisation

The Newcastle upon Tyne Hospitals NHS Foundation Trust

Sponsor details

Freeman Road
High Heaton
Newcastle upon Tyne
England
United Kingdom
NE7 7DN

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tnu-tr.sponsormanagement@nhs.net

Sponsor type

Hospital/treatment centre

Website

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

Publication and dissemination plan

1. Peer-reviewed scientific journals
2. Internal report
3. Conference presentation
4. Publication on a website
5. Submission to regulatory authorities

Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators. Anonymous data from the CRESCENT trial will be made available to other researchers. All requests for data will be reviewed by the Sponsor and the data controllers.

Intention to publish date

31/05/2026

Individual participant data (IPD) sharing plan

The current data sharing plans for this study are unknown and will be available at a later date

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?
HRA research summary			28/06/2023	No	No
Protocol article		29/05/2024	30/05/2024	Yes	No