

# Carbogen for status epilepticus in children trial

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<b>Registration date</b> 27/07/2022	<b>Overall study status</b> Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 30/12/2025	<b>Condition category</b> 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 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](mailto:crescent-trial@liverpool.ac.uk)

# Contact information

**Type(s)**

Scientific

**Contact name**

Dr Rob Forsyth

**ORCID ID**

<https://orcid.org/0000-0002-5657-4180>

**Contact details**

Department of Paediatric Neurology  
Great North Children's Hospital  
Level 3, Clinical Resource Building 2  
Royal Victoria Infirmary  
Newcastle upon Tyne  
United Kingdom  
NE1 4LP

-

[crescent-trial@liverpool.ac.uk](mailto:crescent-trial@liverpool.ac.uk)

**Type(s)**

Principal investigator

**Contact name**

Dr Rob Forsyth

**Contact details**

Department of Paediatric Neurology  
Great North Children's Hospital  
Level 3, Clinical Resource Building 2  
Royal Victoria Infirmary  
Newcastle upon Tyne  
United Kingdom  
NE1 4LP

-

[crescent-trial@liverpool.ac.uk](mailto:crescent-trial@liverpool.ac.uk)

**Type(s)**

Public

**Contact name**

Dr CRESCENT Trial Team

**Contact details**

Liverpool Clinical Trials Centre  
Institute of Child Health  
Alder Hey Children's NHS Foundation Trust  
Liverpool

United Kingdom  
L12 2AP  
-  
crescent-trial@liverpool.ac.uk

## 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<sub>2</sub>: 95% O<sub>2</sub>

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<sub>2</sub>

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?
<a href="#">Protocol article</a>	Participant information sheet	29/05/2024	30/05/2024	Yes	No
<a href="#">HRA research summary</a>			28/06/2023	No	No
<a href="#">Participant information sheet</a>		11/11/2025	11/11/2025	No	Yes
<a href="#">Study website</a>	Study website	11/11/2025	11/11/2025	No	Yes