**Therapeutic hypercapnia after cardiac arrest: a pilot feasibility and safety randomized controlled trial**

*Short title:* Therapeutic hypercapnia after cardiac arrest

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## Lay Summary

Cardiac arrest is a relatively common and devastating event in Australia and New Zealand (ANZ). It is associated with extremely high mortality. A large proportion of those who survive are left with serious neurological disability. Such disability includes memory loss, paralysis and difficulty in thinking and speaking. These deficits often lead to a loss of independence and the need to be admitted to aged-care facilities.

Immediate cardio-pulmonary resuscitation and defibrillation by bystanders has only partly improved the outcome of these patients. For those who survive the immediate phase and are admitted to the intensive care unit, actively decreasing the body temperature to 33-34°C has been shown to protect the brain. Although limited, these results suggest that some interventions after cardiac arrest can improve brain outcome. Perhaps other interventions could lead to similar results and further improve patient’s recovery and quality of life after cardiac arrest.

In a recent observational study in 12,000 ANZ patients who were admitted in ICU after a cardiac arrest, we found that those who had an elevated partial pressure of carbon dioxide (PaCO2) in the 24 hours following the cardiac arrest had a higher chance of having a satisfactory neurological recovery. These patients were 20% more likely to be able to go back home at the end of their hospital stay as compared with those whose PaCO2 was either in the normal or low range. These findings are similar to those seen in previous animal studies. They also make physiological sense: a higher PaCO2 is known to trigger an increase in the amount of blood directed towards the brain. An increase in brain blood flow after a cardiac arrest (a state of no flow) should be logically associated with a higher chance of recovery. However, these findings need to be confirmed by prospective trials before they can be applied to all patients with a cardiac arrest.

PaCO2 is normally controlled by the lungs and its arterial partial pressure is directly related to the rate and amplitude of the breathing process. After a cardiac arrest, patients typically are unconscious or heavily sedated by medication and their breathing process is almost entirely taken care of by a ventilator (breathing machine). In such circumstances, the PaCO2 is determined by the medical team. Currently, a “normal” value for PaCO2 (35-45 mmHg) is targeted by clinicians. However, changing this target value to 50-55 mmHg, would be technically easy to implement and carry no extra cost.

Based on the findings of our retrospective study, on animal studies and logic, we hypothesize that a higher PaCO2 in the first 24 hours after cardiac arrest will be associated with less neurological injury and be feasible and safe. To test this hypothesis, we plan to randomly allocate 100 patients admitted to ICU after cardiac arrest to either “High PaCO2” or “Control” group.

The key outcomes of interest would be whether such trial can be done, whether this therapy appears safe and whether it decreases blood test-based markers of brain injury (brain proteins like neuron specific enolase and S100 protein), indicating that a biological benefit is taking place.

## Aim and hypothesis

**Aims:** To assess the safety, feasibility, and brain biomarker effect of 24 hours of therapeutic hypercapnia in patients admitted to ICU after cardiac arrest.

**Hypothesis**: As compared with standard care (PaCO2 35-45 mmHg), maintaining a high (50-55mmHg) PaCO2 in the 24 hours following a cardiac arrest is feasible, safe and associated with lower neuron specific enolase (NSE) and S-100 protein serum concentration at 24, 48 and 72 hours.

***Primary Objective (efficacy)*:** To compare differences in neuron specific enolase serum concentration between patients allocated to “High” and “Normal” PaCO2 targets in the first 24 hours after intensive care admission for cardiac arrest.

## Background and rationale

Cardiac arrest is relatively frequent in developed countries [[1-3](#_ENREF_1)] and associated with a high morbidity and mortality [[4](#_ENREF_4), [5](#_ENREF_5)]. Most patients do not survive despite resuscitation efforts [[5-7](#_ENREF_5)], and only 40% of those admitted to hospital survive to hospital discharge. Even fewer patients have sufficient neurological recovery to be able to return home [[8](#_ENREF_8)]. This poor neurological outcome is attributed to cerebral ischemia [[9](#_ENREF_9)]. To date, therapeutic hypothermia is the only intervention shown to lead to better neurological outcomes among survivors of out of hospital cardiac arrest [[10](#_ENREF_10)]. However, other modifiable aspects of patient care may also deliver improved neurological outcomes. One such candidate intervention is the maintenance of a higher PaCO2 with the aim of increasing or restoring cerebral perfusion.

Carbon dioxide arterial tension (PaCO2) is one of the major determinants of cerebral blood flow and changes in its partial pressure in the hours following cardiac arrest may be of major importance to cerebral blood flow [[11](#_ENREF_11), [12](#_ENREF_12)]. As resuscitated patients admitted to the intensive care unit (ICU) are mechanically ventilated, full control of PaCO2 should be possible in almost all patients and carry no cost [[11](#_ENREF_11), [12](#_ENREF_12)]. Hence, manipulation of PaCO2 could be an easy and cheap therapeutic intervention in patients admitted to ICU after cardiac arrest.

We recently conducted a large multi-centre cohort study of patients admitted to ICUs in Australia and New Zealand (ANZ) after resuscitation from non-traumatic cardiac arrest (submitted for publication). This study included more than 12,000 patients. We aimed to examine the relationship between arterial carbon dioxide tension and in-hospital mortality and survival to discharge home, a surrogate of neurological outcome. We found that close to 40% of these patients had documented hypercapnia in the first 24 hours of their ICU stay. After correction for potential confounders (Table 1), these patients had significantly greater likelihood of being discharged home than those that did not present such an episode. A nested cohort analysis revealed that the peak PaCO2 occurred in most instances in the first four hours of ICU admission and was independent of baseline characteristics and ICU management processes (Table 1).

**Table 1.** Multiple Logistic Regression model with discharge home for survivors as the dependent variable using risk-of-death no oxygen, treatment limitation, age, year, glucose low, site, admitted source from home, PaCO2 group as variables

|  |  |  |
| --- | --- | --- |
| **Variable** |  **OR (95%CI)** |  **P-Value** |
| Risk of Death (noox) | 0.91(0.88-0.93) | <0.0001 |
| Treatment limitation | 0.85 (0.48-1.51) | 0.41 |
| Age, decile | 1.1 (1.1-1.1) | <0.0001 |
| Year (calendar) | 1.02 (0.99-1.05) | 0.06 |
| Glucose (low) | 1.00 (0.98-1.32) | 0.07 |
| Admit from home | 1.95 (1.66-2.28) | <0.001 |
| Hyper vs hypocapniaNormo vs hypocapniaNormo vs hypercapniaHypercapnia vs normocapnia | 1.36 (1.11-1.66)1.13 (0.93-1.36)0.83 (0.71-0.97)1.20 (1.03-1.41) | 0.0030.210.0020.002 |

The results of this study are consistent with several animal studies [[13](#_ENREF_13), [14](#_ENREF_14)] and make physiological sense. Indeed, PaCO2 is a major determinant of cerebral blood flow and hypercapnia improves cerebral perfusion [[15-17](#_ENREF_15)]. One can therefore logically expect an association between improved cerebral perfusion and improved recovery. To further investigate the possibility that hypercapnia might be beneficial to cerebral recovery after cardiac arrest, we now intend to perform a pilot prospectivefeasibility and safetysingle-centre randomized controlled trial (Phase I).

## Research Plan

*Overall*

All patients with return of spontaneous circulation after resuscitation for cardiac arrest admitted to the emergency department (ED) of the Austin Hospital will be screened for eligibility (see inclusion criteria). Evaluation will be performed in the emergency department for out-of-hospital cardiac arrests or on ICU admission for in-hospital cardiac arrests.

*Inclusion criteria*

* Non-traumatic, in- or out-of-hospital cardiac arrest with successful resuscitation (return of spontaneous circulation)
* Mechanical ventilation
* Delayed consent obtained from next of kin

*Exclusion criteria*

* Spontaneous ventilation
* Imminent withdrawal of medical therapy
* Traumatic cardiac arrest
* Clinical or Computerized Tomography suspicion of raised intra-cranial pressure
* Cardiac arrest secondary to intracranial bleed
* Pregnancy
* Age <18 years
* Severe chronic airflow limitation

Severe metabolic acidosis (pH <7.1 AND base deficit > 6 mEq/L) – that is not corrected in the 1st two hours of ICU management.

*Intervention description:*

Immediately after randomization, the minute ventilation (as defined by the respiratory rate and tidal volume) will be set on the ventilator to aim for target PaCO2 between 50 and 55 mmHg for patients allocated to the intervention (“High PaCO2”) group and between 35 and 45 mmHg for patients allocated to the control (“normal PaCO2” group). To ensure that PaCO2 is and remains within the desired range, PaCO2 will be measured hourly on arterial blood gases and continuous end tidal CO2 (ETCO2) monitoring will be performed. ETCO2 is a measure of the highest alveolar concentration of CO2 at the end of expiration. It is assumed to represent CO2 partial pressure in alveolar gas, which, in normal lungs, closely parallels arterial levels of CO2 [[18](#_ENREF_18)]. Hence, ETCO2, provides a convenient continuous approximation of PaCO2.

At the end of the 24 hours study period, the target PaCO2 will be set to normal (35-45 mmHg) for patients in both groups.

Patients will be followed-up until hospital discharge and at two time points following hospital discharge. For all patients contact will be made 6 months after ICU admission for a phone interview with a standard Glasgow Outcome Score-extended (GOSE) questionnaire. In addition, for Austin Hospital patients that are admitted to the hospital via Ambulance Victoria will have a phone interview with the GOSE, SF-12 and EQ5D quality of life measures.

See Figure 1. For a summary diagram of the patient experience in the study.



**Figure 1.** Summary diagram of patient experience during study

*Study sites*

The participating sites for this study are:

1. Department of Intensive Care, Austin Hospital
	* Site principal investigator – Professor Rinaldo Bellomo
2. Cardiothroacic and Vascular ICU/HDU, Auckland City Hospital
	* Site principal investigator – Dr Shay McGuiness

*Sample size*

Based on previous literature [[19](#_ENREF_19), [20](#_ENREF_20)], we calculated that, in order to be able to demonstrate a 33% change in serum NSE concentration assuming, after log transformation, a standard deviation equal to 40% of the value of the mean, we would need to recruit50 patients in each arm to achieve a power of 80% with statistical significance set at 0.05. As the NSE data are not normally distributed, an approximation and log transformation was used to estimate effect size [[21](#_ENREF_21)].

*Randomization procedure*

Randomization will be by means of sealed envelopes with permuted blocks of variable size. Each envelope will contain a study arm allocation with the PaCO2 target as well as a copy of a simplified version of the study protocol.

*Blinding*

The treatment will be applied in an unblinded fashion. However, laboratory staff analysing blood samples will be blinded to the allocation arm. Evaluation of outcome will also be blinded to treatment allocation.

*Study monitoring*

To confirm separation between the two study groups, the average / median PaCO2 values as well as the area under the curve will be calculated for each patient and compared between the intervention and control group.

All cases with cardiac arrest who were not randomized will be evaluated and baseline characteristics obtained. These data will be compared to those obtained among randomized patients to assess selection bias.

*Data collection*

For all patients, the following variables will be collected:

* Patients characteristics
	+ Demographics
		- Gender
		- Date of birth
		- Admission date
		- Smoking status
	+ Baseline comorbidities
		- Diabetes
		- Hypertension
		- Congestive heart failure
		- Peripheral vascular disease
		- Chronic obstructive airways disease
		- Chronic liver disease
		- Metastatic cancer
		- Lymphoma/leukemia
		- Chronic renal failure (clearance < 30 ml/min)
* Cardiac arrest characteristics
	+ Time from arrest to return of spontaneous circulation (ROSC)
	+ Initial rhythm during arrest
	+ Time from arrest to first ABG
	+ Suspected cause of arrest
	+ Location of arrest (in or out-of-hospital)
* ICU procedures during first 24 hours of admission
	+ Therapeutic hypothermia
	+ Coronary angiography
	+ Nutrition commenced
	+ Bicarbonate infusion
	+ Thrombo-embolic prophylaxis
	+ Vasoactive infusion required (low- mod or high dose)
	+ Recurrent cardiac arrest
	+ Mechanical ventilation data
		- Ventilation mode
		- Set respiratory rate
		- Set tidal volume
		- Positive end-expiratory pressure (PEEP)
* Outcomes
	+ Primary outcome (efficacy): neuron-specific enolase serum concentration in the first 72 hrs (times 0, 24, 48, 72)
	+ Secondary outcomes
		- Confirmatory outcome: S100 protein plasma concentration in the first 72 hours (times 0, 24, 48, 72)
		- Safety outcomes:
			* Acid-base: pH, SIG, BE, % of patients with acidemia (pH<7.3), % of patients with severe acidemia (pH<7.2).
			* Oxygenation: mean PaO2, FiO2, alveolo-arterial gradient, PEEP
			* Arrythmias: incidence and type
			* Results of cardiac echography (evidence for right ventricular failure)
			* Results of cerebral computerized-tomography
			* Clinical signs suggesting raised intra-cranial pressure (bradycardia, mydriasis) or right ventricular failure.
			* Renal: incidence and severity of acute kidney injury as estimated by urinary output, serum creatinine concentration (RIFLE score) and renal replacement therapy requirement
			* Liver: liver function tests including coagulation tests
		- Feasibility outcomes
			* Separation in PaCO2 between two groups
			* Distribution of values for primary and secondary outcome
			* Randomized / Screened patients ratio
			* Consent rate
			* Data completion rate
			* Loss to follow-up rate
			* Recruitment duration
		- General outcomes
			* Total duration of mechanical ventilation
			* Intensive care length of stay
			* Hospital length of stay (date of discharge)
			* Discharge vital status (alive vs dead)
			* Discharge destination (home, other acute hospital, rehabilitation hospital, aged care)
			* Glasgow outcome score-extended (6 months after admission)
			* Through a collaboration with Ambulance Victoria, and data linkage with their Victorian Ambulance Cardiac Registry, we will obtain 12-month quality of life assessments using the GOSE, SF-12, and EQ5D from adult patients or their proxies.

*Sample storage and handling*

Each patient will have a maximum of four blood samples taken to enable analysis of neuron-specific enolase (NSE) and S-100 protein plasma concentration. The time-points for the blood tests all occur during the first 72 hrs (times 0, 24, 48, 72). We only require samples for NSE and S-100 whilst the patient is admitted to the Intensive Care Unit of the treating study site.

Blood sample volumes will be approximately 5ml each. This equates with a total volume of blood being 20ml (4 X 5ml). Samples will be collected in 5ml Lithium Heparin tubes. Each individual patient will be allocated a unique study identifier. This study identifier will be used to link patient data and samples. Each patient will have a series of blood collection tubes that will be labelled with their identifier and time point (times 0, 24, 48, 72 hrs).

Samples will be spun in a centrifuge immediately following collection and the serum portion of the blood stored in Eppendorf tubes. All serum samples will be shipped to and stored in the -80oC freezer located within the Austin Hospital ICU. All samples will be stored together for the duration of the study until transport for batch analysis.

Analysis of blood samples for NSE will be performed at Pathology Clinical Laboratory, Howard Florey Institute, University of Melbourne, Victoria, Australia. Only the re-identified coded blood sample tubes and a sample identifier list will be sent for analysis.

*Data analysis*

Statistical analyses:

This is a feasibility and safety trial comparing two PaCO2 targets in patients admitted to ICU after cardiac arrest. The primary efficacy measure difference in serum concentration of neuron specific enolase. Outcomes will be compared after log transformation where appropriate. Comparisons will be made using t-test and ANOVA for repeated-measures or Wilcoxon rank-signed test and Kruskall-Wallis according to the underlying distribution for continuous data and Chi-square for categorical data. A Kaplan-Meier curve with log-rank test will be performed to further compare in-hospital mortality and rate of discharge home. Logistic regression analysis will also be performed to adjust for baseline imbalances.

Laboratory values:

NSE and S100 will be analyzed by the Florey Institute of Melbourne University, using dedicated ELISA tests (USCN Life Science Inc., United Kingdom).

**Feasibility**

Based on previous admission rates for cardiac arrests each year, approximately 50 patients per year should fulfil the inclusion criteria. Assuming a 60% recruitment rate, we expect that 1.5 years will be needed to complete the study.

A close collaboration with the emergency department will ensure that patients would need be identified as soon as possible after hospital presentation. This should not be an issue as illustrated by the excellent recruitment rates for the ANZICS-CTG endorsed ARISE trial which requires similar interaction with the emergency department and for which our hospital is the second highest recruiter.

The application of the actual intervention is extremely easy as all included patients would have an arterial line allowing serial PaCO2 monitoring and continuous monitoring can be obtained with end tidal CO2.

## Ethical Considerations

*Guiding principles*

This study is to be performed in accordance with the ethical principles of the Declaration of Helsinki (June 1964 and amended 1975, 1983, 1989, 1996, 2000 and Note of Clarification 2002 and 2004), ICH GCP Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with Therapeutic Goods Administration comments and NHMRC National Statement on Ethical Conduct in Research Involving Humans (June 1999).

*Ethical issues of the study*

Patients who will be eligible for this study are mechanically ventilated and critically ill, and require sedative medications for comfort, safety and to facilitate standard life saving ICU procedures. Critical illness commonly leads to an altered mental state which will affect the patient's mental capacity. In addition, their cognitive capacity is temporarily diminished due to a combination of factors such as the severity of their illness and standard intensive care treatments including ventilatory assistance, sedatives and analgesics. The presence of body organ support interventions further delays the return of the patient's ability to make informed decisions during their stay in the intensive care unit.

Patients who will be eligible for this study are mechanically ventilated and critically ill. Immediately after endotracheal intubation, the minute ventilation needs to be set in the ventilator and is thereafter adapted on a regular basis according to the arterial PaCO2 obtained on arterial blood gas analysis. As our retrospective study suggested that the first hours after cardiac arrest were the most critical, the decision about which PaCO2 target is to be prescribed needs to be made urgently.

As a consequence [because of the immediacy of the situation and the urgent need to make a decision about allocation to treatment group] it is proposed to enrol patients in the study without prior informed consent [see paragraphs 4.4.13 and 4.4.14, National Statement on Ethical Conduct in Human Research, at **http://www.nhmrc.gov.au/\_files\_nhmrc/file/publications/synopses/e72-jul09.pdf.**

Consent procedures will be established by the Austin Health Human Research Ethics Committee. Delayed consent will be obtained from the patient proxy, as per and if permitted by local regulations and as approved by local ethics committee, as soon as possible. The participant will be informed about the study as soon as possible and consent obtained for ongoing participation and use of data.

This proposed method of enrolling patients in the study without prior informed consent has been successfully applied in the Austin Hospital ICU associated with the “Sedation practice in intensive care in Australia and New Zealand: A prospective, randomised, controlled pilot trial” [protocol ANZIC-RC/Y5002] (Austin Health REU number – SERP RH HREC/11/Austin/5 – H2011/04247).

*Confidentiality of patient data*

Participants will not be identified by name, and confidentiality of information in medical records will be preserved. All patients’ details will be entered in coded format. The confidentiality of the participant will be maintained unless disclosure is required by law or other regulations.

*Confidentiality of cognitive function data*

No identifiers will be collected or recorded, except for the purposes of contacting patients who have consented to the cognitive assessments. Data linkage with Ambulance Victoria will require the release of participant identifying details. The identifying details that would be released to Ambulance Victoria, only for the purposes of data linkage, would be the participant’s: full name, gender, date of birth, state of residence and date of last contact, i.e. hospital discharge date. For consented patients; names, telephone numbers and addresses will be collected and stored in a locked filing cabinet for the duration of the study. After this time, the identifiable data will be destroyed. All non-identifiable data will be kept for 15 years as per NHMRC guidelines.

*Information and consent documents*

Next-of-kin (Person Responsible) and patient information sheets, and consent forms have been developed based on Austin Health Human Research Ethics Committee requirements and state regulatory requirements. Please see attached delayed patient and next-of-kin (Person Responsible) information sheets and consent forms.

## Patient safety

*Data safety management committee*

This is a single-centre investigator initiated study. There is no independent Data and Safety Monitoring Committee (DSMC) associated with the conduct of this study.

*Adverse events*

Adverse events (AEs) are defined as any untoward medical occurrence in a patient or clinical investigation subject administered an investigational intervention and which does not necessarily have to have a causal relationship with this treatment (adapted from the Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95 July 2000).

It is recognised that the intensive care patient population will experience a number of common aberrations in laboratory values, signs and symptoms due to the severity of the underlying disease and the impact of standard therapies. These will not necessarily constitute an adverse event unless

they require significant intervention or are considered to be of concern in the investigator’s clinical judgement.

In all cases, the condition or disease underlying the symptom, sign or laboratory value should be reported e.g. renal failure rather than hyperkalaemia, and agitation rather than self-extubation.

*Serious adverse events*

SAEs are defined in accordance with the Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95) (July 2000) as any untoward

medical occurrence that:

* Results in death
* Is life-threatening
* Requires inpatient hospitalisation or prolongation of existing hospitalisation
* Results in persistent or significant disability/incapacity
* Is a congenial anomaly/birth defect
* Is an important medical event which may require intervention to prevent one of the previously listed outcomes

*Reporting*

Adverse events and serious adverse events will be recorded on a separate case report form.

SAEs which occur from the time of commencement of study treatment to hospital discharge will be collected and reported to the Austin Health Human Research Ethics Committee within 24 hours of study staff becoming aware of the event.

Minimum information to report will include:

• Patient initials and study number

• Nature of the event

• Commencement and cessation of the event

• An investigator’s opinion of the relationship between study involvement and the event (unrelated, possibly, probably or definitely related).

• Whether treatment was required for the event and what treatment was administered.

## Data handling, retention, storage and destruction

*Data handling*

The case report form (CRF) will be developed by the members of the investigator team as a paper CRF. All data will be collected by members of the investigator team as described in the CRFs from the source data. Information recorded in the CRF should accurately reflect the subject’s medical/ hospital notes and must be completed as soon as it is made available.

The intent of this process is to improve the quality of the clinical study by providing prompt feedback to the Investigators on the progress of the data submitted and to enhance the ability to collect early safety information in a more timely fashion to fully comply with the intent of GCP requirements. Completed CRFs will be stored within the ICU Research Office, Department of Intensive Care, Austin Hospital.

For the cognitive function assessments, the GOSE will be conducted by a member of the investigating team while the patient is still in hospital. Further data collection will be done by receipt of completed patient questionnaires which will be posted back in a reply paid envelope to the Department of Intensive Care, Austin Hospital addressed to the ICU Research Manager, who is a member of the investigating team. The telephone questionnaire GOSE at 6 months follow up will be completed by a member of the investigating team. Finally, the GOSE will be posted to the person responsible and will be mailed back to ICU Research Manager using reply paid envelopes.

*Data retention, storage and destruction*

The data used will be stored electronically in password protected computers located within the ICU Research Office of Austin Health. Paper data and study related documents used in this study will be re-identified and only a master log will be maintained to identify participants and their study data. The log will be locked in a protected office. All data for this audit will be retained for a period of seven years after which all electronic and paper data will be destroyed in accordance with hospital policy in place at the time.

## Publication

It is expected that findings will be disseminated via publication in peer reviewed journal in the critical care literature. Study findings will also be presented at regional, national and international intensive care conferences. Authorship will be determined by the Investigational team with reference to the International Committee of Medical Journal Editors guidelines. Co-authorship with Ambulance Victoria will be stipulated in publications that use data obtained through the collaboration between the investigators and Ambulance Victoria. Only aggregated de-identified patient data will be presented or published.

## Funding and insurance

This is an investigator-initiated study. Funding is provided by the Austin Hospital Special Purpose Fund (Y8016) *Anaesthesia Intensive Care Trust Fund* (AICTF) for the development and completion of this project. Top-up funding is being sought via a competitive grant application. This grant application has been made by the investigating team to the *2013 Research Grant Application* of the Intensive Care Foundation (ICF). Announcement on the success of this grant application will be known at the 2012 Annual Scientific Meeting on Intensive Care held in October, 2012 on behalf of the Australia New Zealand Intensive Care Society (ANZICS) & Australian College of Critical Care Nurses (ACCCN) organisation.

As an investigator-initiated study performed in a public hospital, indemnity insurance will be provided by the public hospital.

##  Trial registration

This study has been registered with the Australian New Zealand Clinical Trial Registry. This is a public access registry. The trial registration number is ANZCTR is: ACTRN1262000690853.

## Research time-line

Proposed research time-line

* July-August 2012: Submit protocol for HREC approval under Non-Drug Study Advisory Committee (NDSAC) process
* August 2013: interim analysis of 25 patients
* May 2014: completion of patient recruitment
* June 2014: statistical analyses and manuscript preparation
* August 2014: manuscript submission

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