Title: The EXACT protocol: a multi-centre, single-blind, randomised, parallel-group, controlled trial to determine whether early oxygen titration improves survival to hospital discharge in adult OHCA patients

Article Type: Original paper

Section/Category: Clinical

Keywords: Oxygen; Hyperoxia; Out-of-hospital cardiac arrest; Heart arrest; Post-resuscitation care

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Order of Authors: Janet E Bray, PhD; Karen Smith, PhD; Cindy Hein, PhD; Judith Finn, PhD; Michael Stephenson; Peter Cameron, PhD; Dion Stub, MBBS, PhD; Hugh Grantham, MD; Paul Bailey, MD; Deon Brink; Natasha Dodge, MPH; Stephen Bernard, MD, PhD

Abstract: Background: Experimental and observational research suggests hyperoxia following resuscitation from cardiac arrest is associated with neurological injury and worse clinical outcomes. This paper describes the rational and design of the EXACT trial. EXACT aims to determine whether reducing oxygen in the acute phase of post-resuscitation care for out-of-hospital cardiac arrest (OHCA) improves survival.

Methods: EXACT is a multi-centre, randomised (1:1), single-blind, parallel trial. Presumed cardiac OHCA cases who achieve a return of spontaneous circulation will be eligible if they are comatose, with an advanced airway and have an oxygen saturation (SpO2) ≥95% on >10L/min (or 100% oxygen). Paramedics will randomised 1,286 eligible cases to receive oxygen therapy targeting an SpO2 of 90-94% (intervention) or 98-100% (control). Study treatment will continue until admission to an intensive care unit or hospital ward. The primary outcome is survival to hospital discharge. Secondary outcomes include 12-month survival and quality of life.

Results: The study has commenced in the Australian state of Victoria, and has enrolled 132 eligible cases to date (63 intervention and 69 control). Further sites are due to commence in 2019, recruitment is expect to take three years.

Discussion: This study will determine if early reduction of oxygen leads to improved outcomes in OHCA. Such a finding is very likely to rapidly change practice and result in many lives saved world-wide.

Trial registration number: NCT03138005.
There are no linked research data sets for this submission. The following reason is given:
No data was used for the research described in the article
Dear Professors Nolan and Parr,

We are pleased to submit the revised EXACT Protocol for your consideration for publication in *Resuscitation*. We have addressed all the reviewer’s comments.

I confirm that all authors have made substantial contributions to all of the following: (1) the conception and design of the study (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

There is no overlap with previous publications and the manuscript, including related data, figures and tables, have not been published previously and the manuscript is not under consideration elsewhere.

Regards,

[Signature]

Associate Professor Janet Bray on behalf of EXACT investigators

Monash University
Response to reviewer:

We thank the reviewer for their comments which have certainly strengthened this manuscript. All comments have been responded to below.

Abstract
- Edit abstract to a structured format with distinct sections for the trial's Aims, Methods (participants, interventions, objectives, measured outcome, randomization, blinding, analysis), Results, Conclusion, and Trial registration number. Since enrollment has already begun, the results section should describe current enrollment data (e.g. number enrolled, randomized, completed).
Response: Abstract has been edited as requested (see paper).

Body
- Background section does not state specific objectives of the proposed trial at the conclusion of the section.
Response: This has been moved from methods to the end of the introduction (see paper).

- Under Trial summary in Methods, the authors mention that the study commenced in December 2017 with 105 patients enrolled to date. Please include a section on preliminary results describing the active timeline of recruitment, your current number of enrolled patients, follow-ups completed, full protocol completions, and any completed preliminary analysis.
Response: We have added the revised numbers enrolled (n=132), protocol deviations due to ineligible enrolments (n=7) to date, and data withdrawals (n=1). We have not performed any analysis to date.

- Consent: Does the protocol require researchers to approach patients' family members or legally authorized representatives (LAR) before the two-months follow-up letter is sent to surviving patients? If not, can the authors please explain the rationale behind this approach? If a patient is deceased or not capable of decision making, lines 254-256 do not mention attempts at consenting next of kin. Since it is customary to approach LARs when patient consent is not feasible, it would be helpful if the authors provide further explanation.
Response: In Victoria, we will not be approaching patients or their Medical Treatment Decision Maker before the two month letter is sent. Nor are we seeking consent from the patient or their next of kin (see edits in the consent section). We have used this approach previously (e.g. RINSE trial –reference in paper) –with only 4/1324 (0.3%) patients or next of kin withdrawing data from the study (added to paper). The Steering Committee and Ethics Committee decided this was the best approach. The approach in other regions participating in EXACT will be based on the recommendations of individual ethics committees. We have also added a paragraph explaining how this decision was reached in the paper:
In choosing this approach the EXACT Steering Committee and The Alfred Human Research Ethics Committee weighed up the pros and cons, including: that Victoria has grounds for a waiver of consent for emergency research; the next of kin (or Medical Treatment Decision Maker) may not be at the scene or available during study intervention; that the next of kin (or Medical Treatment Decision Maker) may not be able or contactable to provide consent; that no further follow-up will occur for deceased patients; that a similar delayed process has been used in previous Victorian prehospital cardiac arrest trials (e.g. RINSE in which 0.3% [4/1202 cases] of patients or next of kin withdrew data), with only a small number of complaints from those contacted; the ability of the next of kin to receive study information at an earlier period; that some next of kin may take solace in the patient’s participation; and minimizing the distress of relatives and next of kin. To date, only one patient enrolled and contacted has requested to have data withdrawn and we have had no contact from any next of kin.

- For more specific guidance, please refer to the CONSORT 2010 checklist on clinical trials
Reporting: http://www.consort-statement.org/
We also used the layout of the Paramedic2 Protocol paper published in Resuscitation.

- Indicate citations by superscript numbers within the text instead of numbers enclosed in parentheses. See References in link.
  https://www.elsevier.com/journals/resuscitation/03009572/guide-for-authors.
Response: This has been updated.

- Line 26. Change "Background" to "Introduction". This section can include a Background and Objectives sections.
  Response: This has been updated and subheadings used.

- Line 40. - "some elements of recommend care" - correct to "recommended care".
  Response: We have changed this to “some guideline recommendations” and added references to American and European guidelines.

- Line 41. "are not based on strong evidence" - Please cite the relevant literature on oxygen delivery.

  Response: Thank you, this has been corrected.

- Line 60. "neurones" - suggest change to "neurons".
  Response: Neurones is the British spelling – which is used by Resuscitation.

- Lines 64-71. Consider reducing the language in this paragraph as the Lines 72-80 describe sufficiently the results needed to illustrate your argument.
  Response: We have removed the detailed description of the experimental study.

- Line 96. "(Table 1)" - it seems that the authors wanted to reference Table 2 instead of Table 1, please revise.
  Response: Thank you, this has been corrected.

- Lines 98-99. It seems that the authors wanted to reference Table 1 instead of Table 2, please revise.
  Response: Thank you, this has been corrected.

- Line 101-108. Please state the entity that is generating the randomization sequence.
  Response: Detailed have been added.
  Trial treatment has been allocated 1:1 in blocks of 10 as per a computer generated randomisation schedule. The schedule was generated by an investigator and is kept securely at Monash University. Randomisation will be stratified by each ambulance service to control for possible differences in paramedic and hospital treatments.

- Lines 179-180. "by a trained data collector using a standardised using" - remove duplicate "using".
  Response: Thank you, this has been corrected.

- Line 194. "DSMC". Please write "Data Safety Monitoring Committee" next to the first abbreviation used in the manuscript.
  Response: Thank you, this has been corrected.

- Line 258. "enrolled pre-hospital" - correct to "enrolled at the pre-hospital stage"
  Response: Thank you, this has been corrected.

- Line 261. "to send patient information sheet" - correct to "to send the patient information sheet".
  Response: Thank you, this has been corrected.

- Line 262. "for 12-month follow-up" - correct to "for the 12-month follow-up".
Response: Thank you, this has been corrected.

- **Line 263. Change "Summary" to "Discussion".**
  Response: Thank you, this has been corrected.

- **Include a Conclusion section after Discussion.**
  Response: A subheading has been added before the final paragraph.

- **Include a Trial Registration section with the registration number.**
  Response: Added. The study is registered at [https://clinicaltrials.gov](https://clinicaltrials.gov) (NCT03138005).
The EXACT protocol: a multi-centre, single-blind, randomised, parallel-group, controlled trial to determine whether early oxygen titration improves survival to hospital discharge in adult OHCA patients.

Authors: Janet E Bray, Karen Smith, Cindy Hein, Judith Finn, Michael Stephenson, Peter Cameron, Dion Stub, Gavin D Perkins, Hugh Grantham, Paul Bailey, Deon Brink, Natasha Dodge, Stephen Bernard on behalf of the EXACT investigators.

Department of Epidemiology and Preventive Medicine, Monash University; Prehospital, Resuscitation and Emergency Care Research Unit, Curtin University; Alfred Hospital; Ambulance Victoria; Department of Community Emergency Health and Paramedic Practice, Monash University; SA Ambulance Service; Flinders University; St John Ambulance Western Australia; Warwick University.

Correspondence: Stephen Bernard, Centre for Research and Evaluation, Ambulance Victoria, 375 Manningham Road, Doncaster, Victoria, 3108, Australia.

Abstract 224

Word count 3247
ABSTRACT

Background: Experimental and observational research suggests hyperoxia following resuscitation from cardiac arrest is associated with neurological injury and worse clinical outcomes. This paper describes the rational and design of the EXACT trial. EXACT aims to determine whether reducing oxygen in the acute phase of post-resuscitation care for out-of-hospital cardiac arrest (OHCA) improves survival.

Methods: EXACT is a multi-centre, randomised (1:1), single-blind, parallel trial. Presumed cardiac OHCA cases who achieve a return of spontaneous circulation will be eligible if they are comatose, with an advanced airway and have an oxygen saturation (SpO₂) ≥95% on >10L/min (or 100% oxygen). Paramedics will randomised 1,286 eligible cases to receive oxygen therapy targeting an SpO2 of 90-94% (intervention) or 98-100% (control). Study treatment will continue until admission to an intensive care unit or hospital ward. The primary outcome is survival to hospital discharge. Secondary outcomes include 12-month survival and quality of life.

Results: The study has commenced in the Australian state of Victoria, and has enrolled 132 eligible cases to date (63 intervention and 69 control). Further sites are due to commence in 2019, recruitment is expect to take three years.

Discussion: This study will determine if early reduction of oxygen leads to improved outcomes in OHCA. Such a finding is very likely to rapidly change practice and result in many lives saved world-wide.

Trial registration number: NCT03138005.
**Keywords:** Oxygen; Hyperoxia; Out-of-hospital cardiac arrest; Heart arrest; Post-resuscitation care
INTRODUCTION

Background

Out-of-hospital cardiac arrest (OHCA) is common and carries a high mortality rate. For example in our region of Australia and New Zealand, there are approximately 25,000 OHCAs per year with only 12% surviving.\(^1\) Post-resuscitation care forms an important link in the chain of survival in these patients, but some guideline recommendations\(^2,3\), such as the delivery of oxygen, are not based on strong evidence.\(^4\)

Currently, in patients who achieve a return of spontaneous circulation (ROSC), paramedics routinely administer 100% oxygen during transport to hospital. This high oxygen delivery often continues for hours in the emergency department (ED), during cardiac catheterisation (if undertaken), and into the intensive care unit (ICU). Once admitted to the ICU, the fraction of oxygen (FiO2) on the ventilator is then decreased to target a partial pressure of oxygen (PaO2) level within the normal range (generally a PaO2 of >70mmHg and an oxygen saturation (SpO₂) >94%).

Experimental and clinical evidence

The use of 100% oxygen for the first hours after resuscitation is largely one of tradition, based on the notion that several hours of hyperoxia might be beneficial in a patient who has suffered profound tissue hypoxia and may also prevent further hypoxic episodes. However, systematic reviews from laboratory studies\(^5\) and observational clinical studies\(^6\) suggest that the administration of 100% oxygen in the hours after ROSC may increase mortality and neurological
injury. The largest observational study in humans found only 19% were normoxic on arrival at ICU, and hyperoxia was independently associated with increased in-hospital mortality.\textsuperscript{7}

Given current evidence on the pathophysiology of reperfusion injury, it is theoretically plausible that hyperoxia may cause biological harm.\textsuperscript{8} In the early period of reperfusion after resuscitation from cardiac arrest, there is a cascade of molecules produced that are known to injure neurones (reperfusion injury). Whilst reperfusion injury mechanism is complex, one of the major contributors to this injury is the generation of oxygen free-radicals, which are further increased by the administration of additional supplemental oxygen.\textsuperscript{9}

\textit{Pilot study}

One issue for the delivery of normoxia in the pre-hospital setting is the accurate titration of oxygen using available equipment. Many EMS insert supraglottic or endotracheal airways during or immediately after OHCA. Ventilation is provided manually using a bag and reservoir with supplemental oxygen at (or above) 10L/min.

To examine the impact of reducing oxygen on patient oxygenation, we conducted a pilot study to test whether prehospital titration of oxygen results in an equivalent number of patients arriving at hospital with a SpO\textsubscript{2}≥94\% (NCT02499042).\textsuperscript{10} We randomised 61 patients to titrated (2-4L/min, approximately 40-70\% oxygen\textsuperscript{11}) oxygen or control (≥10L/min, i.e. 100\% oxygen\textsuperscript{11}). Patients allocated to titrated oxygen were more likely to desaturate (SpO\textsubscript{2}<94\%: 43\% vs. 4\%, \textit{p}=0.001; SpO\textsubscript{2}<90\%: 19\% vs. 4\%, \textit{p}=0.09); however, the majority (81\%) of these desaturations occurred at 2L/min. On arrival at hospital the majority of patients had a SpO\textsubscript{2} ≥94\% (titrated: 90\% vs. control: 100\%) and all patients had a SpO\textsubscript{2} ≥90\%. These data suggested that oxygen
titration post-ROSC is feasible in the prehospital environment, but needs to occur incrementally.

Objectives and design

This paper describes the rationale and design of the EXACT trial (acronym for Reduction of Oxygen After Cardiac Arrest). The EXACT trial is designed as a randomised, controlled, patient-blinded multicentre trial with two parallel groups and a primary endpoint of survival to hospital discharge. The primary objective of EXACT is to determine whether reducing oxygen in the acute phase of post-resuscitation care for OHCA improves survival. Secondary objectives of the trial are to evaluate the effects of targeted oxygen on cardiac and neurological outcomes, and quality of life at 12-months (Table 1).

METHODS

Trial summary

The EXACT trial is funded in Australia by the National Health and Medical Research Council (NHMRC). The design, management, analysis and reporting are independent of the NHMRC. New Zealand and Finland are currently exploring funding. The study commenced in Victoria (at Ambulance Victoria and 13 hospitals in Melbourne), Australia, on the 11th of December 2017, and has currently enrolled 132 eligible patients. To date, there have been 7 protocol deviations due to the enrolment of ineligible patients. Other Australian and international ambulance services are expected to commence in 2019, the study is expected to take four years to complete (including 12-month follow-up). A list of study sites is available from EXACT
investigators. The roles and responsibilities of the EXACT Committees are given in Supplementary Table S1. The study is registered at https://clinicaltrials.gov (NCT03138005).

Eligibility criteria

Inclusion and exclusion criteria are given in Table 2.

Randomisation, allocation and blinding

Patients will be enrolled by attending paramedics trained in the study protocol. These paramedics will determine if the patient is eligible, open a trial envelope and provide pre-hospital trial treatment as per the randomisation card. Randomisation cards, which include a study number and details of the study intervention, are sealed within an opaque envelope.

Trial treatment has been allocated 1:1 in blocks of 10 as per a computer generated randomisation schedule. The schedule was generated by an investigator and is kept securely at Monash University. Randomisation will be stratified by each ambulance service to control for possible differences in paramedic and hospital treatments. It is not feasible to blind paramedics and hospital staff treating the patient. Data collectors will also not be blinded as documented treatment is likely to reflect allocation. However, patients, the study statistician and 12-month data collectors will be blinded to treatment allocation.

Study treatments

Study treatments will begin pre-hospital and continue until hospital ward or ICU admission. A trial summary is provided in Figure 1 and full details, including contingencies for extubation and reintubation, are given in the Supplementary materials.
Immediately after ROSC, the patient will receive the current standard of care (100% oxygen or \(\geq 10\text{L/min}\)) until a satisfactory \(\text{SpO}_2\) trace and reading is achieved.

Patients allocated to “target \(\text{SpO}_2\) 98-100%” will continue to receive \(\geq 10\text{L/min}\) minute or 100% oxygen setting if mechanically ventilated. This treatment will continue to patient handover in the ED. On ED handover, enrolled patients will continue on the pre-hospital oxygen level until connected to a ventilator. The oxygen setting may then be decreased provided \(\text{SpO}_2\) is maintained between 98-100%.

Patients allocated to “target \(\text{SpO}_2\) 90-94%” will have oxygen reduced initially to 4L/minute (i.e. approximately 70% oxygen) or an air mix setting if mechanically ventilated. If the \(\text{SpO}_2\) remains \(\geq 94\%\) for 5 minutes and the patient is being manually ventilated, the oxygen flow rate will be further reduced to 2L/minute (i.e. approximately 46% oxygen) to target an \(\text{SpO}_2\) of between 90-94%. After ED handover, oxygen will be titrated to maintain a target oxygen saturation of 90-94%.

The oxygen flow will be immediately increased to \(\geq 10\text{L/min}\) minute or a Fi02 of 1.0 (i.e. 100%) if: the oxygen saturation falls to <90% at any time; recurrent cardiac arrest occurs; or if the pulse oximeter trace fails to read despite correct placement.

To identify allocation group a plastic adhesive tag will be connected to the airway device to enable the treatment allocation to be readily visible to treating doctors and nurses in the ED after hospital arrival. This tag will not obstruct the visualisation of the airway device and will be removed after arrival in ICU.
The management of all patients in the pre-hospital phase will follow standard post ROSC care such as continual assessment, blood pressure management, 12 Lead ECG, blood glucose monitoring, treating possible causes of the OHCA and notification to the receiving hospital.

The management of all patients after ED arrival and hospital admission will follow the hospital’s standard practices for OHCA management. Typically these include carbon dioxide control, blood pressure control and targeted temperature management. If patients are transferred between participating hospitals, study allocation will continue as per protocol.

Patients transferred to the cardiac catheterisation laboratory will continue to follow oxygen titration treatment as per study allocation (“target SpO₂ 98-100%” or “target SpO₂ 90-94%”).

After arrival in the ICU, the patient will continue on the allocated oxygen treatment until the initial ICU ABG is taken. After this point the intervention phase of the study is concluded and the oxygen treatment will follow the standard practice of the ICU. All subsequent management of the patient is at the discretion of the treating ICU physician.

One-year follow-up

Australian patients surviving to hospital discharge will be contacted by experienced staff at the Study Coordinating Centre (Monash University) 12 months after recruitment. The staff conducting follow-up calls will be blinded to the treatment allocation. Patients or a proxy (i.e. family member) will be invited to provide verbal consent and participate in a telephone interview using the 12-Item Short Form Health Survey (SF-12)⁴², EuroQol (EQ-5D™) health
questionnaire, Glasgow Outcome Scale –extended (GOSE) and modified Rankin Score (MRS).

Sample size

The data from the Victorian Ambulance Cardiac Arrest Registry (VACAR) found that for the year 2013-2014 of the OHCA patients who had ROSC, 35% of those survived to hospital discharge. In the RICH trial, there were 397 patients enrolled and 134 (34%) survived to hospital discharge. Given that the largest observational clinical study found that hyperoxia had a odds ratio of 1.8 for mortality compared with normoxia, the two meta-analyses of the observation studies had odds ratio of 1.4 for improved outcome with normoxia, the sample size for this trial will be powered to detect a much more modest relative improvement in outcome of 25%. The 100% oxygen arm is predicted as having 35% survival rate and the targeted oxygen arm is planned to have 44% survival rate. After adjusting for the interim analysis, the study requires 643 patients per arm with 90% power and restricted $\alpha = 0.049$. We plan to add 10% to this sample size to account for loss to follow up. The overall planned enrolment size will therefore be 1,416 patients. The study is expected to take four years to recruit.

Recruitment

Each ambulance service will monitor attended OHCA patients for missed enrolment and discuss each case with treating paramedics. Newsletters will be sent out regularly to paramedic teams with updates and reminders.
Data management

All pre-hospital and in-hospital patient data will be collected into a secure online database (REDCap). The REDCap database will be hosted on Monash University managed servers in a secure datacentre in Victoria, Australia. All data is encrypted in transit using industry’s standard SSL encryption. Data is backed up nightly and backups are securely stored at a geographically distinct location in Victoria, Australia.

Pre-hospital data will be collected from each ambulance service’s cardiac arrest registries and ambulance patient care records (PCRs). In-hospital data will be collected retrospectively from the enrolled patient’s hospital medical record by trained data collectors using a standardised data dictionary (available from authors). Data includes sociodemographics (e.g. age, sex), arrest features (e.g. witnessed, duration in arrest), pre-hospital clinical data (e.g. airway type, desaturations, and treatments), hospital clinical data (e.g. post-arrest treatments, desaturations), adverse events (e.g. re-arrest during a desaturation) and outcomes (e.g. survival to hospital discharge, neurological outcomes). Due to the large number of sites and available funding, auditing will only occur for participants who experience a serious adverse event.

Final data will be stored at Monash University on a secure password protected server. The server on which the data will be stored will require active directory permissions and will be restricted to the study staff at the Study Coordinating Centre. All data transfers will be via a Secure File Transfer Protocol (SFTP) using Secure Socket Layer (SSL) 128bit encryption. Data transfer, storage and access protocols meets the International (and Australian) ISO27,001 standard for information security.
**Statistical Methods**

**Interim analysis**

One blinded interim analysis will be conducted and reviewed by the Data Safety Monitoring Committee (DSMC) after 50% of participants have been enrolled. The DSMC can request unblinding of data if required. In order to control the overall type I error rate, we will set the alphas using the O’Brien-Fleming approach, such that the $\alpha_1=0.0054$, and $\alpha_2=0.0492$. Sample size has been adjusted (increased by 3 cases in each arm) to account for the interim analysis.

The study will be discontinued at the interim analysis if there are safety concerns related to a group difference in serious adverse events; a survival to hospital discharge difference between the two arms using a strict $p$-value ($p<0.005$) according to the O’Brien-Fleming rule; and results from other published studies show benefit or harm with any of the interventions.

The principal trial analyses of primary and secondary outcomes will be conducted on an intention-to-treat basis (all randomised patients excluding those withdrawing consent for data collection) and in the per-protocol sample (all randomised patients excluding those withdrawing consent and protocol violations). Data analysis will be performed independently by a statistician who is blinded to the allocated intervention arms.

Analysis of the primary and secondary outcomes will be performed using the chi-square test for binary outcomes and T-test for continuous outcomes. Non-parametric variables will be summarised as median ± interquartile range, and groups compared using Mann-Whitney Rank sum tests. Kaplan-Meier methods will be used to assess 12-month survival according to
randomisation assignment. Multivariable analysis of outcomes using logistic or linear regression will be used if there is variation in baseline characteristics. Included co-variates will be determined a priori by the Steering Committee. A detailed statistical plan will be published with the final manuscript. All reported P values will be two-sided.

Subgroup analyses

Primary and secondary outcomes analysis by treatment group will also be examined in the following a priori subgroups: age ≥65 years; sex; witnessed arrest; bystander CPR; witnessed and bystander CPR; initial shockable and non-shockable rhythms; collapse to ROSC >20 minutes; use of drugs for airway insertion; and ambulance service, and for specific aetiologies such as those with and without acute coronary syndromes. Adjusted subgroup analyses will performed using multivariable logistic regression.

Data monitoring

A DSMC comprising experts in clinical trials, biostatistics, emergency and cardiac medicine has been established. The DSMC will monitor accumulated data periodically during the recruitment phase and report to the Steering Committee accordingly. The DSMC will subsequently make recommendations to the steering committee regarding the continuation, termination, or proposed modifications to the study based on the observed effects of the study intervention and adherence to the study protocol. Unless the DMC request cessation of the trial the Steering Committee will not be informed of results of interim analyses performed by the DSMC.

Ethics and consent
The study protocol was originally approved by the Alfred Hospital Human Research Ethics Committee (in Victoria). Protocol modifications will be approved by the Alfred Ethics Committee before approval at other site Ethics Committees.

Consent in Australia

Patients who are eligible for this study will be unconscious following resuscitation after a cardiac arrest and will be unable to provide informed consent. In Australia, the NHMRC Ethics Statement makes provision for delayed or waiver of consent in time-critical interventions within the emergency or critical care setting. There is also a different legal framework in each Australian state allowing for delayed or waiver of consent for research in emergency situations. Justifications for deferred or waived consent in this trial include the requirement for treatment to be administered pre-hospital immediately after patient resuscitation.

In Victoria, where the study has commenced, the study is approved under a waiver of informed consent. However, enrolled patients who survive to hospital discharge are mailed an “Introductory letter” and “Information Sheet for Patients” to advise them of enrolment in the study. For patients who are deceased or discharged from hospital to palliative care, the next of kin is sent a “Condolence letter” with study information. These letters are sent approximately two months after the cardiac arrest to ensure that they have recovered sufficiently. This letter will provide the option for patients and next of kin to call a State Investigator if they: have further questions; wish to OPT-out of the 12 months follow-up (survivors only); or object to enrolment or having data collected. Patients who object to the collection of data will have no further data collected from that time onwards, but data collected to that time will be retained.
In choosing this approach the EXACT Steering Committee and The Alfred Human Research Ethics Committee weighed up the pros and cons, including: that Victoria has grounds for a waiver of consent for emergency research; the next of kin (or Medical Treatment Decision Maker) may not be at the scene or available during study intervention; that the next of kin (or Medical Treatment Decision Maker) may not be able or contactable to provide consent; that no further follow-up will occur for deceased patients; that a similar delayed process has been used in previous Victorian prehospital cardiac arrest trials (e.g. RINSE20 in which 0.3% [4/1202 cases] of patients or next of kin withdrew data), with only a small number of complaints from those contacted; the ability of the next of kin to receive study information at an earlier period; that some next of kin may take solace in the patient’s participation; and minimizing the distress of relatives and next of kin. To date, only one patient enrolled and contacted has requested to have data withdrawn and we have had no contact from any next of kin.

The approach to consent in other regions participating in EXACT will be based on the recommendations of regional ethics committees. Consent procedures for other study regions will be reported in the main trial publication.

Confidentiality

Patients will be enrolled at the pre-hospital stage and allocated a study number. The study number will be used for the collection of all trial data. The patients name, address, phone number and study number will be kept on a separate spreadsheet within each State Study Site—this information is required for study tracking, to send the patient information sheet to patients discharged alive, and for the 12-month follow-up.
DISCUSSION

Previous systematic reviews and recent preliminary clinical data suggests targeting a normal level of oxygen, as opposed to a hyperoxic state, is associated with improved outcomes for OHCA patients. However, the existing level of evidence is not of sufficient quality to definitively change clinical practice.

The International Liaison Committee on Resuscitation (ILCOR) review in 2010 notes that “There is insufficient clinical evidence to support or refute the use of inspired oxygen concentration titrated to arterial blood oxygen saturation in the early care of cardiac arrest patients following sustained ROSC.” The review also identifies the need for prospective randomized controlled clinical trials to compare ventilation with 100% oxygen versus ventilation with inspired oxygen titrated to an arterial blood oxygen in the period after sustained ROSC. The recent 2015 ILCOR review, states that the existing evidence relating to treatment with hyperoxia vs. normoxia post-arrest is of “very low quality” – which is the lowest ranking possible for evidence quality and again identifies the need for high-quality RCTs.

Conclusion

Thus, a Phase 3 study demonstrating a clear benefit is required to change the current practice of continuing 100% oxygen in the early post-arrest period. If the EXACT study demonstrates significantly improved outcomes using an early reduction of oxygen in patients with OHCA, clinical practice is very likely to change rapidly and result in many lives saved world-wide.
Funding

The EXACT study is funded by a project grant from the National Health and Medical Research Council (NHMRC; #APP1107509). The Pre-hospital Emergency Care Australia and New Zealand (PEC-ANZ) NHMRC Centre of Research Excellence (#APP1029983) will supply infrastructure and administrative support. JB and DS are supported by Heart Foundation Fellowships. PC is funded by a NHMRC Fellowship. The funders had no role in the trial design, in the collection or analysis of the data, or in the writing of the manuscript.

Acknowledgments

We would like to acknowledge Dhanya Nambiar for her contribution.

Figure Legend

Figure 1. Outline of the EXACT trial.

REFERENCES


<table>
<thead>
<tr>
<th><strong>Primary Outcome</strong></th>
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<tr>
<td>Survival to hospital discharge.</td>
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<tr>
<th><strong>Secondary Outcomes</strong></th>
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<tr>
<td>Recurrent cardiac arrest requiring chest compressions before ICU admission and not related to withdrawal of life-sustaining treatment</td>
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<tr>
<td>Myocardial injury (cardiac biomarkers, echocardiogram and ST-resolution by 24 hours in those with STEMI)</td>
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<tr>
<td>Incidence of hypoxia (SpO$_2$&lt;90%) before ICU admission</td>
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<td>Neurological outcome (Cerebral Performance Category score) at hospital discharge.</td>
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<tr>
<td>Survival to intensive care unit discharge</td>
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<tr>
<td>Intensive care unit and hospital length of stay</td>
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<tr>
<td>Cause of death during hospital stay (e.g. cardiogenic shock, re-arrest with no ROSC, treatment withdrawn –hypoxic brain injury, brain death)</td>
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<tr>
<td>Quality of life (SF-12 and EQ-5d), neurological outcome (modified Rankin Score), degree of recovery (GOS-E) and survival at 12-months</td>
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Table 2. Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
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<tr>
<td>Adults (age 18 years or older)</td>
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<tr>
<td>Out-of-hospital cardiac arrest of presumed cardiac cause</td>
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<tr>
<td>All cardiac arrest rhythms</td>
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<tr>
<td>Unconscious (Glasgow Coma Scale &lt;9)</td>
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The EXACT protocol: a multi-centre, single-blind, randomised, parallel-group, controlled trial to determine whether early oxygen titration improves survival to hospital discharge in adult OHCA patients.

Authors: Janet E Bray, Karen Smith, Cindy Hein, Judith Finn, Michael Stephenson, Peter Cameron, Dion Stub, Gavin D Perkins, Hugh Grantham, Paul Bailey, Deon Brink, Natasha Dodge, Stephen Bernard on behalf of the EXACT investigators.

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Abstract 224178

Word count 30003247
ABSTRACT

**Background:** Experimental and observational research suggests hyperoxia following resuscitation from cardiac arrest is associated with neurological injury and worse clinical outcomes. This paper describes the rational and design of the EXACT trial. EXACT aims to determine whether reducing oxygen in the acute phase of post-resuscitation care for out-of-hospital cardiac arrest (OHCA) improves survival.

**Methods:** EXACT is a multi-centre, randomised (1:1), single-blind, parallel trial. Presumed cardiac OHCA cases who achieve a return of spontaneous circulation will be eligible if they are comatose, with an advanced airway and have an oxygen saturation (SpO₂) ≥95% on >10L/min (or 100% oxygen). Paramedics will randomised 1,286 eligible cases to receive oxygen therapy targeting an SpO₂ of 90-94% (intervention) or 98-100% (control). Study treatment will continue until admission to an intensive care unit or hospital ward. The primary outcome is survival to hospital discharge. Secondary outcomes include 12-month survival and quality of life.

**Results:** The study has commenced in the Australian state of Victoria, and has enrolled 132 eligible cases to date (63 intervention and 69 control). Further sites are due to commence in 2019, recruitment is expect to take three years.

**Discussion:** This study will determine if early reduction of oxygen leads to improved outcomes in OHCA. Such a finding is very likely to rapidly change practice and result in many lives saved world-wide.

**Trial registration number:** NCT03138005.
The use of 100% oxygen for the first hours after resuscitation is largely based on the perceived benefit of maximising oxygen delivery in patients who have suffered profound hypoxia, and to avoid the risk of further hypoxic events. However, experimental and observational research suggests the associated hyperoxia seen in some cardiac arrest patients may lead to additional neurological injury and worse clinical outcomes. EXACT is a multi-centre, international, randomised (1:1), single-blind, parallel trial which aims to determine whether reducing oxygen administration to target a lower oxygen level as soon as possible in presumed cardiac out-of-hospital cardiac arrest (OHCA) improves survival. Presumed cardiac OHCA cases who achieve a return of spontaneous circulation will be eligible if they are comatose, with an advanced airway in-situ and have a pulse oximeter oxygen saturation (SpO2) ≥95% on 100% or >10L/min of oxygen. Eligible patients will be randomised to receive oxygen therapy targeting an oxygen saturation of either 90-94% (intervention) or 98-100% (control). Study treatment will commence pre-hospital in participating ambulance services and continues in-hospital until admission to an intensive care unit (NCT03138005).

**Keywords:** Oxygen; Hyperoxia; Out-of-hospital cardiac arrest; Heart arrest; Post-resuscitation care
INTRODUCTION

Background

Out-of-hospital cardiac arrest (OHCA) is common and carries a high mortality rate. For example in our region of Australia and New Zealand, there are approximately 25,000 OHCAs per year with only 12% surviving. Post-resuscitation care forms an important link in the chain of survival in these patients, but some elements of guideline recommendations, such as the delivery of oxygen, are not based on strong evidence.

Currently, in patients who achieve a return of spontaneous circulation (ROSC), paramedics routinely administer 100% oxygen during transport to hospital. This high oxygen delivery often continues for hours in the emergency department (ED), during cardiac catheterisation (if undertaken), and into the intensive care unit (ICU). Once admitted to the ICU, the fraction of oxygen (FiO2) on the ventilator is then decreased to target a partial pressure of oxygen (PaO2) level within the normal range (generally a PaO2 of >70mmHg and an oxygen saturation (SpO2) >94%).

Experimental and clinical evidence

The use of 100% oxygen for the first hours after resuscitation is largely one of tradition, based on the notion that several hours of hyperoxia might be beneficial in a patient who has suffered profound tissue hypoxia and may also prevent further hypoxic episodes. However, systematic reviews from laboratory studies and observational clinical studies suggest that the administration of 100% oxygen in the hours after ROSC may increase mortality and neurological
injury. The largest observational study in humans, found only 19% were normoxic on arrival at ICU, and hyperoxia was independently associated with increased in-hospital mortality.\textsuperscript{7}

Given current evidence on the pathophysiology of reperfusion injury, it is theoretically plausible that hyperoxia may cause biological harm.\textsuperscript{8} In the early period of reperfusion after resuscitation from cardiac arrest, there is a cascade of molecules produced that are known to injure neurones (reperfusion injury). Whilst reperfusion injury mechanism is complex, one of the major contributors to this injury is the generation of oxygen free-radicals, which are further increased by the administration of additional supplemental oxygen.\textsuperscript{9}

\textit{Pilot study}

One issue for the delivery of normoxia in the pre-hospital setting is the accurate titration of oxygen using available equipment. Many EMS insert supraglottic or endotracheal airways during or immediately after OHCA. Ventilation is provided manually using a bag and reservoir with supplemental oxygen at (or above) 10L/min. An experimental study, titrating oxygen using different oxygen input flows into typical prehospital resuscitation equipment demonstrated that a setting of >8L/min provided close to 100% oxygen, whereas 4L/min of oxygen (at a tidal volume of 600mL and a ventilation rate of 10L/minute) delivered approximately 70% oxygen and 2L/min delivered approximately 40% oxygen.

To examine the impact of reducing oxygen on patient oxygenation, we conducted a pilot study to test whether prehospital titration of oxygen results in an equivalent number of patients arriving at hospital with a \textit{SpO}_2≥94\% (NCT02499042).\textsuperscript{10}
We randomised 61 patients to titrated (2-4L/min, approximately 40-70% oxygen) oxygen or control (≥10L/min, i.e. 100% oxygen). Patients allocated to titrated oxygen were more likely to desaturate (SpO2<94%: 43% vs. 4%, p=0.001; SpO2<90%: 19% vs. 4%, p=0.09); however, the majority (81%) of these desaturations occurred at 2L/min. On arrival at hospital the majority of patients had a SpO2 ≥94% (titrated: 90% vs. control: 100%) and all patients had a SpO2 ≥90%.

These data suggested that oxygen titration post-ROSC is feasible in the prehospital environment, but needs to occur incrementally.

**Objectives and design**

**This paper describes the rationale and design of the EXACT trial (acronym for Reduction of Oxygen After Cardiac Arrest). The EXACT trial is designed as a randomised, controlled, patient-blinded multicentre trial with two parallel groups and a primary endpoint of survival to hospital discharge. The primary objective of EXACT is to determine whether reducing oxygen in the acute phase of post-resuscitation care for OHCA improves survival. Secondary objectives of the trial are to evaluate the effects of targeted oxygen on cardiac and neurological outcomes, and quality of life at 12-months (Table 1).**

**METHODS**

**Trial summary**

The EXACT trial (acronym for Reduction of Oxygen After Cardiac Arrest) is funded in Australia by the National Health and Medical Research Council (NHMRC). The design, management, analysis and reporting are independent of the NHMRC. New Zealand and Finland are currently exploring
The study commenced in Victoria (at Ambulance Victoria and 13 hospitals in Melbourne), Australia, on the 11th of December 2017, and has currently enrolled 105-139 eligible patients. To date, there have been 7 protocol deviations due to the enrolment if ineligible patients. Other Australian and international ambulance services are expected to commence in 2019, the study is expected to take four years to complete (including 12-month follow-up). A list of study sites is available from EXACT investigators. The roles and responsibilities of the EXACT Committees are given in Supplementary Table S1. The study is registered at https://clinicaltrials.gov (NCT03138005).

The EXACT trial is designed as a randomised, controlled, patient-blinded multicentre trial with two parallel groups and a primary endpoint of survival to hospital discharge. The primary aim of the trial is to determine whether reducing oxygen administration to target a normal SpO2 level as soon as possible in comatosed adults with ROSC following a presumed cardiac OHCA improves survival rates at the time of hospital discharge. Secondary aims of the trial are to evaluate the effects of targeted oxygen on cardiac and neurological outcomes, and 12-month quality of life (Table 1). The roles and responsibilities of the EXACT Committees are given in Supplementary Table S1.

Eligibility criteria

Inclusion and exclusion criteria are given in Table 2.

Randomisation, allocation and blinding
Patients will be enrolled by attending paramedics trained in the study protocol. These paramedics will determine if the patient is eligible, open a trial envelope and provide pre-hospital trial treatment as per the randomisation card in addition to usual care. Randomisation cards, which include a study number and details of the study intervention, are sealed within an opaque envelope.

Trial treatment has been will be allocated 1:1 in blocks of 10 as per a computer generated randomisation schedule. The schedule was generated by an investigator and is kept securely at Monash University by pre-randomised cards. The cards will be randomised by computer-generated code into blocks of ten, allocated a study number and sealed within an opaque envelope that conceals the treatment allocation. Randomisation will be stratified by each ambulance service to control for possible differences in paramedic and hospital treatments. It is not feasible to blind paramedics and hospital staff treating the patient. Data collectors will also not be blinded as documented treatment is likely to reflect allocation. However, patients, the study statistician and 12-month data collectors will be blinded to treatment allocation.

Study treatments

Study treatments will begin pre-hospital and continue until hospital ward or ICU admission. A trial summary is provided in Figure 1 and full details, including contingencies for extubation and reintubation, are given in the Supplementary materials.

Immediately after ROSC, the patient will receive the current standard of care (100% oxygen or ≥10L/min) until a satisfactory SpO2 pulse oximeter trace and SpO2 reading is achieved.
Patients allocated to “target SpO\textsubscript{2} 98-100%” will continue to receive ≥10/L minute or 100% oxygen setting if mechanically ventilated. This treatment will continue to patient handover in the ED. On ED handover, enrolled patients will continue on the pre-hospital oxygen level until connected to a ventilator. The oxygen setting may then be decreased provided SpO\textsubscript{2} is maintained between 98-100%.

Patients allocated to “target SpO\textsubscript{2} 90-94%” will have oxygen reduced initially to 4L/minute (i.e. approximately 70% oxygen) or an air mix setting if mechanically ventilated. If the SpO\textsubscript{2} remains ≥94% for 5 minutes and the patient is being manually ventilated, the oxygen flow rate will be further reduced to 2L/minute (i.e. approximately 46% oxygen) to target an SpO\textsubscript{2} of between 90-94%. After ED handover, oxygen will be titrated to maintain a target oxygen saturation of 90-94%.

The oxygen flow will be immediately increased to ≥10/L minute or a FiO\textsubscript{2} of 1.0 (i.e. 100%) if: the oxygen saturation falls to <90% at any time; recurrent cardiac arrest occurs; or if the pulse oximeter trace fails to read despite correct placement.

To identify allocation group a plastic adhesive tag will be connected to the airway device to enable the treatment allocation to be readily visible to treating doctors and nurses in the ED after hospital arrival. This tag will not obstruct the visualisation of the airway device and will be removed after arrival in ICU.

The management of all patients in the pre-hospital phase will follow standard post ROSC care such as continual assessment, blood pressure management, 12 Lead ECG, blood glucose monitoring, treating possible causes of the OHCA and notification to the receiving hospital.
The management of all patients after ED arrival and hospital admission will follow the hospital’s standard practices for OHCA management. Typically these include carbon dioxide control, blood pressure control and targeted temperature management. If patients are transferred between participating hospitals, study allocation will continue as per protocol.

Patients transferred to the cardiac catheterisation laboratory will continue to follow oxygen titration treatment as per study allocation (“target SpO\textsubscript{2} 98-100%” or “target SpO\textsubscript{2} 90-94%”).

After arrival in the ICU, the patient will continue on the allocated oxygen treatment until the initial ICU ABG is taken. After this point the intervention phase of the study is concluded and the oxygen treatment will follow the standard practice of the ICU. All subsequent management of the patient is at the discretion of the treating ICU physician.

**One-year follow-up**

Australian patients surviving to hospital discharge will be contacted by experienced staff at the Study Coordinating Centre (Monash University) 12 months after recruitment. The staff conducting follow-up calls will be blinded to the treatment allocation. Patients or a proxy (i.e. family member) will be invited to provide verbal consent and participate in a telephone interview using the 12-Item Short Form Health Survey (SF-12)\textsuperscript{12}, EuroQol (EQ-5D\textsuperscript{TM}) health questionnaire\textsuperscript{13}, Glasgow Outcome Scale –extended (GOSE)\textsuperscript{14} and modified Rankin Score (MRS)\textsuperscript{15}.

**Sample size**
The data from the Victorian Ambulance Cardiac Arrest Registry (VACAR) found that for the year 2013-2014 of the OHCA patients who had ROSC, 35% of those survived to hospital discharge.\textsuperscript{16} In the RICH trial\textsuperscript{17,18}, there were 397 patients enrolled and 134 (34%) survived to hospital discharge. Given that the largest observational clinical study found that hyperoxia had a odds ratio of 1.8 for mortality compared with normoxia,\textsuperscript{8} and the two meta-analyses of the observation studies had odds ratio of 1.4 for improved outcome with normoxia\textsuperscript{6,19}, the sample size for this trial will be powered to detect a much more modest relative improvement in outcome of 25%. The 100% oxygen arm is predicted as having 35% survival rate and the targeted oxygen arm is planned to have 44% survival rate. After adjusting for the interim analysis, the study requires 643 patients per arm with 90% power and restricted $\alpha = 0.049$. We plan to add 10% to this sample size to account for loss to follow up. The overall planned enrolment size will therefore be 1,416 patients. \textbf{The study is expected to take four years to recruit.}

\textit{Recruitment}

Each ambulance service will monitor attended OHCA patients for missed enrolment and discuss each case with treating paramedics. Newsletters will be sent out regularly to paramedic teams with updates and reminders.

\textit{Data management}

All pre-hospital and in-hospital patient data will be collected into a secure online database (REDCap). The REDCap database will be hosted on Monash University managed servers in a secure datacentre in Victoria, Australia. All data is encrypted in transit using industry's standard

\textbf{11}
SSL encryption. Data is backed up nightly and backups are securely stored at a geographically distinct location in Victoria, Australia.

Pre-hospital data will be collected from each ambulance service’s cardiac arrest registries and ambulance patient care records (PCRs). In-hospital data will be collected retrospectively from the enrolled patient’s hospital medical record by a trained data collector using a standardised data dictionary (available from authors). Data includes sociodemographics (e.g. age, sex), arrest features (e.g. witnessed, duration in arrest), pre-hospital clinical data (e.g. airway type, desaturations, and treatments), hospital clinical data (e.g. post-arrest treatments, desaturations), adverse events (e.g. re-arrest during a desaturation) and outcomes (e.g. survival to hospital discharge, neurological outcomes). Due to the large number of sites and available funding, auditing will only occur for participants who experience a serious adverse event.

Final data will be stored at Monash University on a secure password protected server. The server on which the data will be stored will require active directory permissions and will be restricted to the study staff at the Study Coordinating Centre. All data transfers will be via a Secure File Transfer Protocol (SFTP) using Secure Socket Layer (SSL) 128bit encryption. Data transfer, storage and access protocols meets the International (and Australian) ISO27,001 standard for information security.

Statistical Methods

Interim analysis
One blinded interim analysis will be conducted and reviewed by the Data Safety Monitoring Committee (DSMC). After 50% of participants have been enrolled. The DSMC can request unblinding of data if required. In order to control the overall type I error rate, we will set the alphas using the O’Brien-Fleming approach, such that the $\alpha_1=0.0054$, and $\alpha_2=0.0492$. Sample size has been adjusted (increased by 3 cases in each arm) to account for the interim analysis.

The study will be discontinued at the interim analysis if there are safety concerns related to a group difference in serious adverse events; a survival to hospital discharge difference between the two arms using a strict p-value ($p<0.005$) according to the O’Brien-Fleming rule; and results from other published studies show benefit or harm with any of the interventions.

The principal trial analyses of primary and secondary outcomes will be conducted on an intention-to-treat basis (all randomised patients excluding those withdrawing consent for data collection) and in the per-protocol sample (all randomised patients excluding those withdrawing consent and protocol violations). Data analysis will be performed independently by a statistician who is blinded to the allocated intervention arms.

Analysis of the primary and secondary outcomes will be performed using the chi-square test for binary outcomes and T-test for continuous outcomes. Non-parametric variables will be summarised as median ± interquartile range, and groups compared using Mann-Whitney Rank sum tests. Kaplan-Meier methods will be used to assess 12-month survival according to randomisation assignment. Multivariable analysis of outcomes using logistic or linear regression will be used if there is variation in baseline characteristics. Included co-variates will be
determined a priori by the Steering Committee. A detailed statistical plan will be published with the final manuscript. All reported P values will be two-sided.

Subgroup analyses

Primary and secondary outcomes analysis by treatment group will also be examined in the following a priori subgroups: age ≥65 years; sex; witnessed arrest; bystander CPR; witnessed and bystander CPR; initial shockable and non-shockable rhythms; collapse to ROSC >20 minutes; use of drugs for airway insertion; and ambulance service, and for specific aetiologies such as those with and without acute coronary syndromes. Adjusted subgroup analyses will performed using multivariable logistic regression.

Data monitoring

A Data Safety Monitoring Committee (DSMC) comprising experts in clinical trials, biostatistics, emergency and cardiac medicine has been established. The DSMC will monitor accumulated data periodically during the recruitment phase and report to the Steering Committee accordingly. The DSMC will subsequently make recommendations to the steering committee regarding the continuation, termination, or proposed modifications to the study based on the observed effects of the study intervention and adherence to the study protocol. Unless the DMC request cessation of the trial the Steering Committee will not be informed of results of interim analyses performed by the DSMC.

Ethics and consent
The study protocol was originally approved by the Alfred Hospital Human Research Ethics Committee (in Victoria). Protocol modifications will be approved by the Alfred Ethics Committee before approval at other site Ethics Committees via Regional Committees.

**Consent in Australia**

Patients who are eligible for this study will be unconscious following resuscitation after a cardiac arrest and will be unable to provide informed consent. This study constitutes emergency research. In Australia, the NHMRC Ethics Statement makes provision for delayed or waiver of consent in time-critical interventions within the emergency or critical care setting. There is also a different legal framework in each Australian state allowing for delayed or waiver of consent for research in emergency situations. Justifications for deferred or waived consent in this trial include the requirement for treatment to be administered pre-hospital immediately after patient resuscitation.

In Victoria, where the study has commenced, the study is approved under a waiver of informed consent. However, enrolled patients who survive to hospital discharge will be mailed an “Introductory letter” and “Information Sheet for Patients” to advise them of enrolment in the study. For patients who are deceased or discharged from hospital to palliative care, the next of kin is sent a “Condolence letter” with study information. These letters will be sent approximately two months after the cardiac arrest to ensure that they have recovered sufficiently. This letter will provide the option for patients and next of kin to call a State Investigator if they: have further questions; wish to OPT-out of the 12 months follow-up (survivors only); or object to enrolment or having data collected. Patients who object to the
collection of data will have no further data collected from that time onwards, but data collected
to that time will be retained.

In choosing this approach the EXACT Steering Committee and The Alfred Human Research
Ethics Committee weighed up the pros and cons, including: that Victoria has grounds for a
waiver of consent for emergency research; the next of kin (or Medical Treatment Decision
Maker) may not be at the scene or available during study intervention; that the next of kin (or
Medical Treatment Decision Maker) may not be able or contactable to provide consent; that no
further follow-up will occur for deceased patients; that a similar delayed process has been used
in previous Victorian prehospital cardiac arrest trials (e.g. RINSE20 in which 0.3% [4/1202 cases]
of patients or next of kin withdrew data), with only a small number of complaints from those
contacted; the ability of the next of kin to receive study information at an earlier period; that
some next of kin may take solace in the patient’s participation; and minimizing the distress of
relatives and next of kin. To date, only one patient enrolled and contacted has requested to
have data withdrawn and we have had no contact from any next of kin.

The approach to consent in other regions participating in EXACT will be based on the
recommendations of regional ethics committees. Consent procedures for other study regions
will be reported in the main trial publication.

For patients who are deceased or discharged from hospital to palliative care, the decision to
send a condolence letter with study information will be based on the recommendations of
individual ethics committees.

Confidentiality
Patients will be enrolled at the pre-hospital stage and allocated a study number. The study number will be used for the collection of all trial data. The patient's name, address, phone number and study number will be kept on a separate spreadsheet within each State Study Site—this information is required for study tracking, to send the patient information sheet to patients discharged alive, and for the 12-month follow-up.

**SUMMARY DISCUSSION**

Previous systematic reviews\textsuperscript{5, 6} and recent preliminary clinical data\textsuperscript{21, 22} suggest that targeting a normal level of oxygen, as opposed to a hyperoxic state, is associated with improved outcomes for OHCA patients. However, the existing level of evidence is not of sufficient quality to definitively change clinical practice.\textsuperscript{4}

The International Liaison Committee on Resuscitation (ILCOR) review in 2010 notes that “There is insufficient clinical evidence to support or refute the use of inspired oxygen concentration titrated to arterial blood oxygen saturation in the early care of cardiac arrest patients following sustained ROSC.”\textsuperscript{23} The review also identifies the need for prospective randomized controlled clinical trials to compare ventilation with 100% oxygen versus ventilation with inspired oxygen titrated to an arterial blood oxygen in the period after sustained ROSC. The recent 2015 ILCOR review, states that the existing evidence relating to treatment with hyperoxia vs. normoxia post-arrest is of “very low quality”—which is the lowest ranking possible for evidence quality and again identifies the need for high-quality RCTs.\textsuperscript{4}

**Conclusion**
Thus, a Phase 3 study demonstrating a clear benefit is required to change the current practice of continuing 100% oxygen in the early post-arrest period. If the EXACT is study demonstrates significantly improved outcomes using an early reduction of oxygen in patients with OHCA, clinical practice is such a finding is very likely to change rapidly and result in many lives saved world-wide.

Funding

The EXACT study is funded by a project grant from the National Health and Medical Research Council (NHMRC; #APP1107509). The Pre-hospital Emergency Care Australia and New Zealand (PEC-ANZ) NHMRC Centre of Research Excellence (#APP1029983) will supply infrastructure and administrative support. JB and DS are supported by Heart Foundation Fellowships. PC is funded by a NHMRC Fellowship. The funders had no role in the trial design, in the collection or analysis of the data, or in the writing of the manuscript.

Acknowledgments

We would like to acknowledge Dhanya Nambiar for her contribution.

Figure Legend

Figure 1. Outline of the EXACT trial.


<table>
<thead>
<tr>
<th>Primary Outcome</th>
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<td>Survival to hospital discharge.</td>
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<td>Secondary Outcomes</td>
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<tr>
<td>Recurrent cardiac arrest requiring chest compressions before ICU admission and not related to withdrawal of life-sustaining treatment</td>
</tr>
<tr>
<td>Myocardial injury (cardiac biomarkers, echocardiogram and ST-resolution by 24 hours in those with STEMI)</td>
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<tr>
<td>Incidence of hypoxia (SpO$_2$&lt;90%) before ICU admission</td>
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<tr>
<td>Neurological outcome (Cerebral Performance Category score) at hospital discharge.</td>
</tr>
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<td>Survival to intensive care unit discharge</td>
</tr>
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<td>Intensive care unit and hospital length of stay</td>
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<td>Cause of death during hospital stay (e.g. cardiogenic shock, re-arrest with no ROSC, treatment withdrawn −hypoxic brain injury, brain death)</td>
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<td>Quality of life (SF-12 and EQ-5d), neurological outcome (modified Rankin Score), degree of recovery (GOS-E) and survival at 12-months</td>
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Table 2. Inclusion and exclusion criteria

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<td>All cardiac arrest rhythms</td>
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<td>“Not for Resuscitation” order or Advanced Care Directives in place</td>
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<td>Cardiac arrest due to drowning, trauma or hanging</td>
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Out-of-hospital cardiac arrest (OHCA) patients assessed for eligibility

Randomisation (N=1416)

Allocated to “target SpO₂ 90-94%”

Allocated to “target SpO₂ 98-100%”

Intervention phase concluded after first ABG in ICU
Oxygen adjusted according to standard practice of ICU

Primary outcome:
Survival to hospital discharge

12 month follow-up

Exclusion criteria
Known/suspected pregnancy
Dependent on others for ADLs
NFR order or advance care directive
Pre-existing oxygen therapy (i.e. COPD)
OHCA (trauma, drowning or hanging)
The EXACT protocol: a multi-centre, single-blind, randomised, parallel-group, controlled trial to determine whether early oxygen titration improves survival to hospital discharge in adult OHCA patients.

Authors: Janet E Bray, Karen Smith, Cindy Hein, Judith Finn, Michael Stephenson, Peter Cameron, Dion Stub, Gavin D Perkins, Hugh Grantham, Paul Bailey, Deon Brink, Natasha Dodge, Stephen Bernard on behalf of the EXACT investigators.

Conflicts of interest: none