

Participant Information Sheet/Consent Form – Person Responsible

Interventional Study – Person responsible consenting on behalf of participant –continue participation

Title	Targeted therapeutic mild hypercapnia after resuscitated cardiac arrest: A phase III multi-centre randomised controlled trial
Short Title	TAME Cardiac Arrest
Protocol Number	ANZIC-RC/SB001
Project Sponsor	The ANZIC Research Centre
Local Principal Investigator	Dr Hergen Buscher
Location	St Vincents Hospital, Sydney

Part 1 What does participation involve?

1 Introduction

The participant has been enrolled as a participant in this research project with the approval of the Austin Health Human Research Ethics Committee and in accordance with NSW Law without obtaining consent in advance due to the participant's condition at the time the participant was enrolled.

As the 'Person Responsible' for the participant, you are invited to consider the participant's continued participation in the TAME Cardiac Arrest study. The TAME Cardiac Arrest study will evaluate the ability of higher carbon dioxide levels in the blood to reduce brain damage in out-of-hospital cardiac arrest patients admitted to the intensive care unit. The participant was enrolled into this study as the participant experienced an out-of-hospital cardiac arrest and was then brought to the intensive care unit for ongoing medical treatment.

Before you decide if you wish for the participant can continue to participate in this study, it is important for you to understand why the research is being done, what it will involve and how the participant's personal information will be used. Please take the time to read the following information carefully and if appropriate discuss it with the participant's friends, family and their doctor. One or more of our team will go through the information sheet with you and answer any questions you have. Please ask questions about anything that you do not understand or want to know more about.

If you don't wish the participant to continue to take part, they don't have to. They will receive the best possible care whether or not they take part. If during the course of the study the participant becomes capable they may withdraw from this study in their own right.

2 What is the purpose of this research?

Cardiac arrest is the sudden, unexpected loss of heart function, breathing and consciousness. Many cardiac arrest survivors experience ongoing difficulties in thinking and performing their normal social activities. A possible reason why survivors experience such difficulties may be related to low brain blood flow and low oxygen levels experienced during the early period after the heart has been restarted.

The major normal controller of blood flow to the brain is the level of carbon dioxide in blood. Increased levels of blood carbon dioxide (hypercapnia) markedly increase brain blood flow. Following a cardiac arrest aiming for normal carbon dioxide levels in the blood may not be enough to achieve and maintain enough blood flow and oxygen delivery to the brain. At this point in time, emergency and intensive care doctors do not know if aiming for 'about 20% higher than normal' (mild hypercapnia) carbon dioxide levels in the blood is better than standard care (normal carbon dioxide levels) to help the brain recover in cardiac arrest patients whose heart has been restarted and who are on a breathing machine in the intensive care unit.

Based on strong earlier studies, the purpose of this study is to evaluate the ability of higher carbon dioxide levels to reduce brain damage. This will be done by comparing brain performance 6 months after cardiac arrest in two groups: those treated with '20% higher than normal' carbon dioxide levels and those treated with 'normal' carbon dioxide levels (current standard care). The findings of this study will then allow doctors to make informed decisions about which target blood carbon dioxide level is better for their patients.

This study will include 1,700 patients with out-of-hospital cardiac arrest patients whose heart could be restarted and who required support with a breathing machine and who were admitted to an intensive care in one of multiple countries or regions such as Australia, New Zealand, Western Europe, Ireland, Scandinavia, North America and the United Kingdom.

This study has been funded by the Australian National Health and Medical Research Council (NHMRC) and the Irish Health Research Board (HRB) and is supported by the ANZIC Research Centre of Monash University, Melbourne, Australia.

3 What does participation in this research involve?

If you agree to the participant's continuation of participation in this study, you will be asked to sign this Person Responsible Consent Form and you will be given a copy to keep on behalf of the Participant.

In the hospital

Following admission to hospital and inclusion in the study the participant was randomly assigned (like tossing a coin) by a computer to receive one of two interventions.

This means that the participant had an equal (50/50) chance of being allocated to:

1. Standard care (Targeted normocapnia) (TN)
- Or
2. Targeted therapeutic mild hypercapnia (TTMH)

If the participant was allocated to the TN protocol the participant was sedated and received breathing support from a breathing machine (mechanical ventilator). Regular and routine arterial blood gas samples and end-tidal (breathed out) carbon dioxide levels were then used to guide respiratory rate adjustments to help maintain a blood carbon dioxide range of 35-45 mmHg for 24 hours after randomisation.

If the participant was allocated to the TTMH protocol the participant was sedated and received breathing support from a breathing machine (mechanical ventilator). Regular and routine arterial blood gas samples and end-tidal (breathed out) carbon dioxide levels were then used to guide respiratory rate adjustments to help maintain a blood carbon dioxide range of 50-55 mmHg for 24 hours after randomisation.

After the 24-hour intervention period, the participant's treating clinician determined the level of carbon dioxide in the participant's blood to target. All other standard hospital practices for the management of resuscitated cardiac arrest patients were performed in accordance with existing best practice protocols and international guideline recommendations. The decision to discharge the participant from the ICU was made by the participant's treating ICU doctors.

All post-ICU management was at the discretion of the participant's ward-based treating doctors.

Following discharge from hospital

Following the patient's discharge from hospital a research coordinator will meet with you (face-to face, videolink or via telephone) on three occasions: 30 days, 6 months and 2 years after the date the participant started the study. The purpose of these calls is to see how the participant is recovering. At each time point the research coordinator will also ask you (or a nominated person) some standard questions about the participant's quality of life which should only take about 10 minutes. If there are any concerns about the participant's health or wellbeing during one of these telephone calls the research coordinator will discuss these with you and may also inform the participant's general practitioner (GP) of the concerns.

Linkage of healthcare records

Healthcare record linkage will also be conducted 6 months after the participant's participation in the study to assess the health services the participant has used over a specified time period. 6 months after the participant's participation in the TAME Cardiac Arrest study, the ICU study staff will send the participant's personal details (name, address, date of birth and medical record number) to the ANZIC Research Centre. These details will then be sent offsite to state and national data linkage units who will link the participant's personal information with state and national databases to assess the health services the participant has used over a specified time period. The type of databases to be accessed will be hospital admission databases, registries of births deaths and marriages, and the Australian bureau of statistics. Then all of your identifying information (name, address, date of birth and medical record number) will be removed and will be forwarded to the research team at The ANZICS Research Centre for analysis.

Optional biomarker sub-study

You are invited to consent to the participant's participation in an optional biomarker sub-study. The biomarker sub-study is looking at blood tissue samples from participants to understand why people react differently following a cardiac arrest. This could be related to their genetic material or the extent of brain or heart injury or inflammation that has occurred in the early post-resuscitation period. The biomarker sub-study will not provide any benefit to the participant. This biomarker sub-study may help us to understand this better and allow us to develop a test that will inform best practice decisions in the future. There are no additional risks to the participant participating in the biomarker sub-study.

We have taken blood tissue samples from the participant at admission to hospital and at 24 h, 48 h, and 72 hours (approximately 6 ml or 1 teaspoon at each time-point) from an existing drip line after the participant was enrolled to the TAME Cardiac Arrest study.

You will be asked to provide additional consent for the collection of the participant's blood tissue samples obtained during the research project.

The participant's blood tissue samples obtained for the purpose of this research project will be transferred to the biobank of the Integrated Biobank of Luxembourg (IBBL), Luxembourg. Once the participant's blood

tissue samples are transferred to IBBL they will be analysed for the purposes of this study only. After all blood tissue samples have been analysed they will be destroyed in accordance with existing protocols in place at the time at IBBL.

4 Does the participant have to take part in this research project?

Continuing participation in this study is entirely voluntary. If you do not wish to for the participant to take part, you do not have to. If you decide to allow the participant to continue participation and later change your mind, you are free to withdraw their participation from the project at any stage. Whatever your decision, it will not affect the participant's relationship with the staff caring for the participant.

If you wish to withdraw the participant from the study, you can do so at any time without having to give a reason. If you do withdraw the participant from the study, study related information may have already been sent to the coordinating centre and it may not be possible to have that information recalled or deleted: information not recalled or deleted will still be used.

If you stop the participant from being part of this study, the study doctor or one of the ICU staff members will talk to you about any medical issues regarding the stopping the participant's participation. Even if you stop the participant's participation in the study, the re-identified information obtained for the whole study period is critical to providing doctors with information on whether or not one or other of the study interventions is better for their patients. We would request that we continue to collect data on treatment received whilst in intensive care and information on the participant's health status for up to 180 days from the day the participant entered the study.

5 What are the alternatives to participation?

If you decide not to allow the participant to participate in this study, the participant will continue to be provided with the best care for the participant's condition. Usual medical treatment for resuscitated cardiac arrest patients may include the targeting of one arterial carbon dioxide range over another while patients are sedated and on a breathing machine.

6 What are the possible benefits of taking part?

While we intend that this research study furthers medical knowledge and may determine the best treatment of resuscitated cardiac arrest patients in the future, it may not be of direct benefit to the participant.

7 What are the possible risks and disadvantages of taking part?

All medical procedures involve some risk of injury. In addition, there may be risks associated with this study that are presently unknown or unforeseeable. In spite of all reasonable precautions, the participant might develop medical complications from participating in this study.

There are known risks associated with the manipulation of carbon dioxide levels in the blood. Very low carbon dioxide levels in the blood can result in blood vessels becoming narrower (vasoconstriction) and reducing blood flow to the brain. High carbon dioxide levels in the blood can result in blood vessels becoming wider (vasodilation) and increasing blood flow to the brain. Prolonged states of abnormally low or high carbon dioxide levels in the blood are rare. As the participant will be in the intensive care

unit when the study intervention is applied, the participant will be closely monitored and treated immediately if any effects were to occur.

If at any point during the study the participant's study doctor feels it is in the participant's best interests not to continue receiving the study intervention; or if during the study there is evidence to suggest beyond reasonable doubt that one study intervention is more beneficial than the other then the participant's involvement in the study may be stopped.

8 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, the participant's study doctor will tell you about it and discuss with you whether you want to the participant to continue participation in the research project. If you decide to withdraw the participant, the study doctor will make arrangements for the participant's regular health care to continue. If you decide to continue the participant's participation in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in the best interests of the participant to be withdrawn from the research project. If this happens, he/she will explain reasons and arrange for the participant's regular health care to continue.

9 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

- Unacceptable side effects
- The treatment being shown not to be effective
- The treatment being shown to work or not need further testing
- Decisions made by local regulatory/health authorities.

Part 2 How is the research project being conducted?

10 What will happen to information about the participant?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about the participant for this specific research study only. Any information obtained in connection with this research study that can identify the participant will remain confidential. Data will remain confidentially stored in research offices at St Vincents Hospital. The offices will be securely locked and only accessible by the research team. Electronic data will be kept securely on a password protected database. Any data sent electronically to the central database located at The ANZIC Research Centre, Monash University will be coded, and only the ICU research team at St Vincents Hospital will have the list that can link your identity to the study code. The participant's information will only be used for the purpose of this research study and it will only be disclosed with your permission, except as required by law. The study data will be securely stored for 15 years following publication of the study results and then destroyed, as required by law.

The participant's health records and any information obtained relevant to the study during the research are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities, The ANZIC Research Centre, Monash University, the institution relevant to this Participant

Information Sheet, St Vincents Hospital, or as required by law. By signing the Consent Form, you authorise the release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

It is anticipated that the results of this research will be published and or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that the participant cannot be identified, except with your permission. Identifiable information will not be made public in any form so that confidentiality of the participant is maintained. The study database will contain information from all study participants, but not anything that can identify the participant as an individual. This information may be made available to other researchers. If this happens the participant's identity will be protected and the participant will not be identified or contacted by other researchers who request access to the study database.

Results of the study will be provided to you, if you wish.

Information about participation in this research may be recorded in the participant's health records. In accordance with relevant Australian state and federal privacy laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

11 Complaints and compensation

If the participant suffers any injuries or complications as a result of this study, you should contact the study doctor on behalf of the participant as soon as possible, who will assist you in arranging appropriate medical treatment for the participant.

The participant may have a right to take legal action to obtain compensation for any injuries or complications resulting from the participant's participation in the study. Compensation may be available if the participant's injury or complication is caused by the study intervention, or by the negligence of any of the parties involved in the study. If the participant receives compensation that includes an amount for medical expenses, the participant will be required to pay for the participant's medical treatment from those compensation monies.

If the participant is not eligible for compensation for their injury or complication under the law, but are eligible for Medicare, then the participant can receive any medical treatment required for their injury or complication free of charge as a public patient in any Australian public hospital.

12 Who is organising and funding the research?

The Coordinating Principal Investigator for this study is A/Prof Glenn Eastwood, Department of Intensive Care, Austin Hospital, Melbourne, Victoria. This research has received funding from the National Health and Medical Research Council of Australia and the Irish Health Research Board.

All monies will be administered through Monash University and the ANZIC Research Centre and are directed to run the study at the coordinating centre and participating hospitals. This money pays the **[insert name of local site]** for the work done by its staff in this study. No money is paid directly to individual researchers.

13 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the Austin Health Human Research Ethics Committee [**Reference Number HREC/17/Austin/209**].

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

14 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if the participant has any medical problems which may be related to the participant's involvement in the project (for example, any side effect), you can contact the principal study doctor on 02 83822036 or any of the following people:

Clinical contact person

Name	<i>Claire Reynolds</i>
Position	<i>ICU Research Coordinator</i>
Telephone	<i>02 83822174</i>
Email	Claire.reynolds@svha.org.au

For matters relating to research at the site at which the participant is participating, the details of the local site complaints person are:

Complaints contact person

Position	<i>Research Office Manager</i>
Telephone	<i>[02 83824960</i>
Email	svhs.research@svha.org.au

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Austin Health Human Research Ethics Committee
HREC Executive Officer	Ms Chelsea Webster
Telephone	03 9496 4090
Email	ethics@austin.org.au

Consent Form - Person responsible consenting on behalf of participant - to enrol or continue



Title	Targeted therapeutic mild hypercapnia after resuscitated cardiac arrest: A phase III multi-centre randomised controlled trial
Short Title	TAME Cardiac Arrest
Protocol Number	ANZIC-RC/SB001
Project Sponsor	The ANZIC Research Centre
Local Principal Investigator	Dr Hergen Buscher
Location	St Vincents Hospital

Declaration by Person Responsible

- I have read the Person Responsible Information Sheet or someone has read it to me in a language that I understand.
- I understand the purposes, procedures and risks of the research described in the project.
- I give permission for the participant's doctors, other health professionals, hospitals or laboratories outside this hospital to release information to **St Vincents Hospital** concerning the participant's condition and treatment for the purposes of this project. I understand that such information will remain confidential.
- I have had an opportunity to ask questions and I am satisfied with the answers I have received.
- I freely agree to the participation of the participant in this research project as described and understand that I am free to withdraw my consent to the participation of the participant at any time during the study without affecting their future health care.
- I understand that I will be given a signed copy of this document to keep.
- I consent to the collected blood samples obtained from the participant being used for the Biomarker Sub study (please tick one box):

YES	☐
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NO	☐
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Name of Participant (Please print) _____	
Name of Person Responsible (please print) _____	
Signature _____	Date _____

Declaration by Study Doctor/Senior Researcher[†]

I have given a verbal explanation of the research project, its procedures and risks and I believe that the person responsible has understood that explanation.

Name of Study Doctor/ Senior Researcher [†] (please print) _____	
Signature _____	Date _____

[†] A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

I understand that, if I decide to discontinue the study treatment for the participant, they may be asked to attend follow-up to allow collection of information regarding their health status. Alternatively, a member of the research team may request the participant's permission to obtain access to their medical records for collection of follow-up information for the purposes of research and analysis.

Form for Withdrawal of Participation –

Person responsible withdrawing on behalf of participant



Title

Targeted therapeutic mild hypercapnia after
resuscitated cardiac arrest: A phase III multi-centre
randomised controlled trial

Short Title

TAME Cardiac Arrest

Protocol Number

ANZIC-RC/SB001

Project Sponsor

The ANZIC Research Centre

Local Principal Investigator

Dr Hergen Buscher

Location

[Insert local site name] St Vincents Hospital Sydney

Declaration by Person Responsible

As the person responsible for _____ [Insert Participant's name] I wish to withdraw them from participation in the above research project and understand that such withdrawal will not affect their routine treatment, their relationship with those treating them or their relationship with St Vincents Hospital, Sydney

Name of Person Responsible (Please print) _____	
Relationship of Person Responsible to Participant _____	
Signature _____	Date _____

Consent provided to use data collected up to the date of withdrawal: Yes ☐ No ☐

Consent provided to use biological samples collected up to the date of withdrawal: Yes ☐ No ☐

Consent provided to access your medical record to obtain information of health status: Yes ☐ No ☐

Consent provided to contact the participant at 30 days, 180 days and 2 years after starting the study to allow collection of health status information: Yes ☐ No ☐

In the event the person responsible of the participant decided to withdraw verbally, study doctor/senior researcher to give a description of the circumstances below:

Declaration by Study Doctor/Senior Researcher[†]

I have given a verbal explanation of the implications of withdrawal of the participant from the research project and I believe that the person responsible has understood that explanation.

Name of Study Doctor/ Senior Researcher [†] (please print) _____	
Signature _____	Date _____

[†] A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.