The CPR, pre-hospital ECPR and early reperfusion study: A Target Trial Emulation (CHEER4 TTE)

Clinical Trial Registration:	TBC	
Chief Investigator:	Dr Sacha Richardson The Alfred Hospital Level 2, 541 St Kilda Road Melbourne VIC 3004 Telephone: +61 431 383 180 Email: sacha.richardson@alfred.org.au	
Co-Investigators:	Dr Natalie Kruit Prof Ary Serpa A/Prof Mark Dennis A/Prof David Anderson Prof Steve Bernard Prof Brian Burns A/Prof Mark Dennis Dr Joshua Ihle A/Prof Hergen Buscher	Dr Patrick Joyce Dr Ziad Nehme Dr Judit Orosz Dr Ary Serpa Dr Tim Southwood Prof Andrew Udy A/Prof Aidan Burrell Ms Sandra Ware
Coordinating Centre:	Australian and New Zealand Intensive Care Research Centre School of Public Health and Preventive Medicine, Monash University 553 St Kilda Road, Melbourne, Victoria 3004, Australia Telephone: +61 3 9903 0343 Fax: +61 3 9903 0071 Email: anzicrc@monash.edu ANZIC-RC Project Manager, Phoebe McCracken Mobile: +61 458 154 740 Email: phoebe.mccracken@monash.edu	

CONTENTS

1. ABBREVIATIONS

AE	Adverse event
ANZIC-RC	Australian and New Zealand Intensive Care Research Centre
ARR	Absolute Risk Reduction
CHEER 3	The CPR, pre-hospital ECPR and early reperfusion study
CI	Confidence Interval
CPR	Cardiopulmonary Resuscitation
CRF	Case Report Form
CTG	Clinical Trials Group
ECMO	Extracorporeal Membrane Oxygenation
ECPR	Extracorporeal Cardiopulmonary Resuscitation
EVIDENCE	Efficacy and value in expedited out of hospital arrest care with end tidal CO2 ECPR
EMS	Emergency Medical Service
EXCEL	The Australian and New Zealand Extracorporeal Membrane Oxygenation ECMO Registry
HEMS	Helicopter Emergency Medical Services
HREC	Human Research Ethics Committee
ICU	Intensive Care Unit
mCPR	Mechanical Cardiopulmonary Resuscitation
NHMRC	National Health and Medical Research Council
NS	National Statement on the Ethical Conduct of Research in Humans
OHCA	Out of Hospital Cardiac Arrest
PI	Principal Investigator
PRECARE	Pre-Hospital ECPR for refractory cardiac arrest
QOL	Quality of life
RCT	Randomised Controlled Trial
ROSC	Return of spontaneous circulation
SAE	Serious adverse event
TTE	Target Trial Emulation
VACAR	Victorian Ambulance Cardiac Arrest Registry
VECMOS	Victorian ECMO Service

2. LAY DESCRIPTION

Cardiac arrest (where the heart suddenly stops beating effectively), affects over 25,000 Australians each year and is the most common cause of death in otherwise healthy adults. When a cardiac arrest occurs in a patient outside of hospital it is called an Out of Hospital Cardiac Arrest (OHCA). Traditional management of cardiac arrest includes cardiopulmonary resuscitation (CPR). Even with the best CPR only 10% of OHCA patients survive to hospital discharge. Patients who do not get their heart beating again quickly, termed refractory OHCA, have very poor outcomes where less than 5% survive.

Extracorporeal membrane oxygenation (ECMO) is a portable heart lung bypass machine which enables blood to be pumped around the body when the heart is not functioning well. It protects the brain and body organs, whilst the heart gets treated or recovers. When ECMO is used during cardiac arrest it is called ECMO-CPR (ECPR).

The use of ECPR for refractory cardiac arrests has increased substantially and survival rates up to 40% in refractory cardiac arrests have been published. Owing to the resources and technical skills required, ECPR is only offered in a few select hospitals. The best outcomes for ECPR occur when the time from arrest to being placed on the ECMO machine is minimized – ideally less than 60 minutes. The time taken to respond to a 000 call, provide initial CPR and then extricate and transport a patient to a hospital capable of ECPR makes meeting these times extremely challenging.

Prehospital ECPR occurs when specially trained doctors and paramedics take ECMO to the patient at the scene of the cardiac arrest. This has been shown to increase access to patients, reduce time from cardiac arrest to ECMO support and potentially improve outcomes. Both Melbourne and Sydney teams are trialing prehospital ECPR. As yet there are no high-quality studies comparing pre-hospital ECPR to conventional resuscitation. We seek to conduct a trial to assess outcomes for patients who have received prehospital ECPR and those who received conventional resuscitation therapies.

3. SYNOPSIS

Title	The CPR, preHospital ECPR and Early Reperfusion study: A Target Trial Emulation
Short Title	CHEER4 TTE
Objective	To determine whether prehospital ECPR increases survival to hospital discharge in patients with refractory cardiac arrest, as compared with standard care including salvage hospital based ECPR
Hypothesis	Prehospital ECPR is associated with an increased hospital survival in patients with refractory out of hospital cardiac arrest, as compared with standard care
Design	Retrospective observational target trial emulation study using registry data
Sample Size	300-500
Population	Adult patients with refractory OHCA
Selection Criteria	***Inclusion Criteria*** 1. Adult patients 18-70 years old 2. Witnessed cardiac arrest 3. Bystander CPR 4. Refractory cardiac arrest (defined by failure to achieve sustained ROSC by >20 mins post initiation of CPR) 5. Initial cardiac rhythm VF, VT or PEA 6. Within the hours of prehospital ECPR service operation (i.e. Monday to Friday 0900-1700) ***Exclusion Criteria*** 1. Initial cardiac rhythm asystole 2. ROSC with sustained recovery 3. Unable to reach the patient and commence cannulation within 45 minutes of onset of arrest. 4. Evidence of/suspected end stage disease: • Severe disability impairing activities of daily living • End-stage organ – cardiac, liver, lung, renal • Other life-limiting diseases e.g. malignancy, terminal illness • Advance health care directive (not for resuscitation) 5. Time periods of advanced public health restrictions in Victoria or NSW due to COVID-19
Study Procedures	Patients in NSW and Victorian OHCA registries will be assigned to two different arms: • A prehospital ECPR strategy • Conventional cardiac arrest strategy (with +/- hospital based salvage ECPR)
Prehospital ECPR Strategy	Prehospital ECPR patients will be identified from the CHEER3 study (Victoria) and PRECARE Study (NSW) databases, and additional data will be obtained from the EXCEL registry

Conventional Cardiac Arrest Strategy	Conventional cardiac arrest strategy patients will be identified from VACAR, the EVIDENCE Study and NSW OHCA Registry Data Linkage Project. Patients who meet our inclusion and exclusion criteria will be matched to the prehospital ECPR strategy patients
Subgroups	1. A comparison of prehospital patients with conventional CPR patients who underwent hospital based ECPR 2. A comparison of outcomes for different presenting rhythms (VT/VF,PEA) 3. Duration of CPR above and below the median time 4. Greater Melbourne and Sydney vs 45 minutes from ECPR baseline
Common treatment	All intra-arrest and post-arrest care follow guidelines based on the Australian and New Zealand Council of Resuscitation recommendations, supplemented by the Victorian ECMO Service (VECMOS) guidelines within Victoria, and Agency for Clinical Innovation ECMO Clinical Practice Guidelines in NSW
Outcomes	**Primary outcome measure** Survival to hospital discharge **Secondary outcome measures** 1. Low flow time (time from arrest to ECPR flow) 2. ICU length of stay 3. Mechanical ventilation days 4. The number of patients a cerebral performance category (CPC) of 1 or 2 at hospital discharge 5. Rates of organ and tissue donation in non-survivors 6. ECMO complications, including major bleeding episodes and blood culture positive sepsis 7. Long term outcomes, including 6 and or 12-month survival and quality of life (QOL)
Study Duration	6 months

4. STUDY AMDINISTRATIVE STRUCTURE

4.1 Coordinating and Data Management Centre

Australian and New Zealand Intensive Care Research Centre, Monash University.

Role:

- Management of human research ethics committee applications and ongoing reports as required
- Development and assistance with protocol, case report and other study related documents
- Protocol training of investigators, research coordinators and trial team
- Organisation of investigators meeting
- Liaise with funding bodies and key stakeholders as required
- Data analysis and collaborations on publications

4.2 Executive Committee

4.2.1 Responsibilities:

- Day to day management of the project
- General trial management issues
- Development and approval of final documents such as protocol
- Liaison with coordinating centre
- Funding applications

4.2.2 Members:

Dr Sacha Richardson
A/Prof Aidan Burrell
A/Prof Mark Dennis
Dr Natalie Kruit
Dr Paddy Joyce
Dr Ary Serpa Neto
Ms Phoebe McCracken

4.3 Management Committee

4.3.1 Responsibilities:

- Overseeing data analysis
- General study management issues
- Provide clinical insight
- Approval of manuscripts

4.3.2 Members

Dr Sacha Richardson
Dr Natalie Kruit
A/Prof Aidan Burrell
A/Prof Mark Dennis
A/Prof Brian Burns
Prof Ary Serpa
A/Prof David Anderson
Prof Steve Bernard
Dr Joshua Ihle
A/Prof Hergen Buscher
Dr Patrick Joyce
Dr Ziad Nehme
Dr Judit Orosz
Dr Ary Serpa
Dr Tim Southwood
Prof Andrew Udy
Ms Sandra Ware
Ms Phoebe McCracken
Mr Hugh Burrill

5. BACKGROUND AND RATIONALE

5.1 Background

Out of hospital cardiac arrest (OHCA) is a major public health problem in Australia

OHCA is the leading cause of death in otherwise healthy adults [1]. Each year, it effects over 25 000 Australians and only 1/10 will survive to hospital discharge [2]. In Victoria, data from the Victorian Cardiac Arrest Registry shows that there were 6,934 OHCA events attended by Ambulance Victoria paramedics in 2020-2021 [3]. In 2981 patients where there was an attempt at resuscitation, only 4 in 10 had return of spontaneous circulation (ROSC), and overall 9% survived. In the subgroup of patients who do not get ROSC after 15-20 minutes of resuscitation - termed refractory OHCA – neurologically favourable survival occurs in just 2% [4]. The annual economic impact from OHCA is vast – estimated at over AUS$2 billion per year - comparable to the productivity loss from all cancers combined [5].

Conventional cardiopulmonary resuscitation (CCPR) is only effective early post arrest

OHCA involves the sudden cessation of the heartbeat, usually occurring due to a blocked coronary artery. Without an effective heartbeat, the patient immediately becomes unconscious and stops breathing. Irreversible hypoxic brain injury occurs after about five minutes unless resuscitation is commenced. Conventional CPR begins with chest compressions by bystanders at the scene. Following the arrival of emergency services, advanced life support (ALS) begins where CPR is continued and defibrillation and appropriate airway management[6] is added. The majority of patients undergoing CCPR that achieve ROSC will do so in the first 15 minutes[7], and therefore quality improvement programs that target the quality and performance of CPR have been developed – termed High Performance CPR[8]. However, despite the implementation of such programs, beyond 15 minutes it becomes highly ineffective and new strategies for treating refractory OHCA are urgently needed.

Extracorporeal membrane oxygenation (ECMO) is highly effective at restoring the circulation in OHCA

CCPR provides approximately 10-40% of usual resting cardiac output, so the brain and vital organs remain vulnerable to inadequate blood supply[9]. ECMO is a novel solution to this problem. With ECMO, the patient is connected to an external blood pump and oxygenator that provide an artificial circulation. When commenced during cardiac arrest with CPR ongoing, it is termed Extracorporeal Cardiopulmonary Resuscitation (ECPR). Plastic catheters are inserted rapidly into the femoral artery and vein under ultrasound guidance and then are connected to the circuit, pump and oxygenator. Once connected, it is effective at supplying the body with 3-4L/min blood flow, which is equivalent to 100% of resting cardiac output, adequate to restore oxygenation to the tissues and organs. Once supported on ECMO, clinicians then have time to determine the cause of the OHCA[10]. If a blocked coronary artery is suspected, the patient can safely undergo a coronary angiogram. In most patients placed on ECMO it is possible to get the heart beating again once ECMO blood flow has been established. Once the underlying cause is treated and the heart has returned to near-normal function, the ECMO tubes can be removed. The patient is managed in the ICU until neurological recovery has occurred or, if testing confirms significant neurological injury, palliative care is instituted. Importantly, the outcomes after ECPR appear to be binary – most people either die or survive well, with very few people surviving with severe brain injury.

The current outcomes for hospital based ECPR

Hospital based ECPR is the most commonly used model for delivering ECPR for OHCA[11]. Here, suitable patients are identified at the scene, a mechanical CPR(mCPR) device is fitted, the patient is loaded into an ambulance, and then they are rapidly transported to the nearest ECMO capable emergency department for consideration of institution of ECPR. The CHEER Study, completed by our group in 2015 was one of the first hospital based ECPR studies worldwide[12]. Eleven patients were transported to The Alfred Hospital with mechanical CPR in progress. Of these, 9 were placed on ECMO and 3 of these had a good outcome at hospital

discharge. This study, although small and observational, has been cited over 600 times, and led to the availability of mechanical CPR devices to all metropolitan intensive care ambulances across Victoria.

The CHEER study has now been replicated in many other systems, including NSW [13]. A consistent finding from these studies is that the low flow time, defined as the time from arrest to initiation of ECPR, is a key determinate of survival with good neurological function[14]. Longer periods of CCPR prior to ECPR are associated with worse clinical outcomes, while earlier initiation is associated with higher survival rates[15]. Most international guidelines recommend against starting ECPR in patients in cardiac arrest for over 60 minutes[11]. Three randomised clinical trials (RCT) of hospital based ECPR for OHCA have subsequently been conducted. The ARREST trial from the USA was the first RCT of hospital ECPR[16]. In this study, 32 eligible patients were transported after 3 shocks at scene, arriving at the ECMO centre within 45 minutes of the onset of cardiac arrest. Patients were randomised to either ECPR or continued CCPR. The survival to hospital discharge was dramatically improved in the ECMO group (43% versus 7%, ARR 36%, 95% CI 3.7-59.2%), demonstrating that early ECMO is beneficial, however the rapid time to initiate ECPR in this study has not been replicated elsewhere.

The second major RCT was the PRAGUE OHCA trial[17]. This study randomised 256 patients with refractory OHCA to either rapid transportation to an ECPR capable emergency department versus transportation only after further resuscitation at the scene. The intervention resulted in an 11-minute time difference to hospital arrival, although overall CPR times were still prolonged (49 vs 60 minutes respectively). Although the primary outcome was not statistically different, with 39 patients (31.5%) in the early transport group compared with 29 (22.0%) who had continued CPR surviving to 180 days with good neurologic outcome (Odds Ratio, 1.63 [95% CI, 0.93 to 2.85]; p=0.09), several secondary outcomes, such as 30-day neurological recovery suggested potential benefit from the earlier transport.

The most recent RCT was the INCEPTION trial[40]. This study randomised 134 patients with refractory OHCA to receive ECPR in the hospital or conventional CPR. The intervention group had a lower than expected survival with favourable neurologic outcome at 30 days of 20% which was not significantly greater than the control group with 16 %. However, these results need to be interpreted with caution for a number of reasons. Firstly only 46/70 (65%) of patients randomised to ECPR received the intervention. Furthermore, the median interval to commencement of ECMO was much longer than prior trials at 74 mins from onset of arrest (IQR 63-87) which may have significantly diluted the effect of the intervention.

5.2 The limitations of hospital based ECPR for OHCA

There are four main constraints with hospital based ECPR:

1. The requisite extrication, loading and transportation time for patients during cardiac arrest delays ECPR initiation. Extricating and loading patients onto a stretcher, then transporting them – which can involve complex logistics such as navigating stairs – can delay transport to hospital. In the recently published CHEER 2 study, the average time from 000 call to hospital arrival was 64 minutes[18]. As such, many patients arrived at the hospital outside of the 60-minute time window and were ineligible for ECPR[2].
2. Transportation of a patient while CPR is ongoing may reduce the quality of CPR. The movement of patients during CPR creates many challenges which can impair the quality of the CPR. Poor quality CPR has been shown to worsen survival[9]. The prioritisation of quick loading may also undermine the initial delivery of high-performance CPR by paramedics.
3. The 60-minute cut off also reduces the geographical area and population that can be covered by hospital based ECPR. There is currently only a relatively small area of metropolitan Melbourne and Sydney around the active ECPR hospitals where patients may be transported within the time cut offs. Many patients who might otherwise meet ECPR criteria are outside of these areas and are ineligible, worsening inequality of healthcare access.
4. Maintaining multiple hospital based ECPR teams “at the ready” is resource intensive, as multiple hospitals must maintain a full complement of staff on call for relatively infrequent events. It also dilutes expertise.

In summary, while existing data are supportive of the provision of hospital based ECPR over conventional CPR, in cities where transport times are routinely >60 minutes[8,9,10], there are significant challenges to the effective, equitable and efficient use of this technology. The key question to consider is whether ECMO initiated at the scene will reduce time to initiation of ECPR and improve clinical outcomes.

5.3 The rationale for prehospital ECPR

Prehospital ECPR is where the ECMO initiation team is rapidly transported to the patient on scene while CPR is ongoing to initiate ECMO. Scene based ECPR potentially addresses the major limitations of hospital based ECPR:

1. Low flow time can be drastically reduced by bringing the intervention to the patient. The team can be rapidly driven to the patient while CPR is still ongoing. With no need to load the patient, the paramedic/EMS team with the patient can focus on the delivery of high-performance CPR.
2. A larger geographical area can be covered by one highly mobile ECPR team. This will improve access for disadvantaged people living further away from ECMO capable hospitals. Current experience has shown over three quarters of metropolitan Melbourne can be comfortably covered by 25 minutes (lights and sirens) drive from The Alfred Hospital (which is centrally located). Modelling completed in Sydney shows that scene based ECMO would potentially quadruple the population currently served by hospital based ECPR[19].
3. A single mobile team requires a smaller number of staff to train and roster, potentially reducing the overall costs, making it more sustainable, and ensures staff are well exposed to the procedure.

5.3.1 International success with prehospital ECPR

Scene based ECPR has been undertaken in Paris, France since 2011[20]. A French study reported the outcomes of 156 patients placed on ECMO between 2011 and 2015. There were 114 patients in refractory arrest placed on ECMO with cannulation commencing after 30 minutes of CPR and these were compared to 42 placed on ECMO with cannulation commencing after 20 minutes of CPR at scene. The probability of survival to ICU discharge or day 28 with good neurological function was significantly higher in patients placed on ECMO sooner: 29% vs 8% ($p<0.001$). When combining stringent patient selection with an aggressive strategy, the probability of survival in patients with a shorter CPR duration increased to 38%. Our systematic review[21] of scene based ECPR identified four other small case studies of prehospital ECMO including Canada[22], Japan[23] and France[24], although the small numbers precluded performing a metanalysis.

5.3.2 The CHEER3 and PRECARE scene based ECPR pilot results are promising

Over the last three years, The Alfred Hospital in collaboration with Ambulance Victoria, have undertaken a prospective prehospital ECPR pilot study. We have undertaken hundreds of hours of training, simulation, protocol refinement, transport equipment modification, and have a team of over 15 fully trained members providing the service. The first ten patients with scene based ECPR have been published in the CHEER3 paper[41]. The average time from cardiac arrest "000 call" to ECMO team scene arrival was 27 minutes (range 9-37 minutes), with ECMO flow established 50 minutes (range 35-62 minutes) after "000 call". This has reduced the average time to initiate ECMO by 26 minutes compared to hospital initiation over the past 8 years[18]. Out of the ten patients, four (40%) have been discharged home with near complete recovery. In addition, we have shown this model is highly mobile, covering over three quarters of Melbourne's geographic area within a 30-minute drive time, and staff have been able to maintain a very high level of skill and training with regular exposure and daily simulation. To date the prehospital ECPR program in Melbourne has initiated support for 27 patients with refractory cardiac arrest. In NSW, the PRECARE prehospital ECPR program was initiated in 2022 and has now enrolled >15 patients. This model has incorporated an intensive training program of prehospital physicians, geospatial modelling, and has found to be feasible and is growing.

5.3.3 Significance

Given the impressive survival seen in the Paris observational study, the substantial reduction in low flow times seen in our pilot studies, and the ongoing low survival with standard care, and the economic imperative to avoid cost-ineffective interventions, we propose a Target Emulation Trial to determine the estimated

effectiveness of performing prehospital ECMO during refractory out of hospital cardiac arrest as compared to standard care, including hospital-based salvage ECPR. Prehospital ECPR studies are underway in Michigan, USA and London, UK (SUB30 NCT03700125). These small pilot observational studies are unlikely to change global practice. There is one RCT underway in the Netherlands (NCT04620070 ON-SCENE). This study is comparing prehospital ECPR (delivered by Helicopter Emergency Medical Services (HEMS) teams) with standard care (which includes the possibility of ECPR). This study is using 4 HEMS services and covers both urban and rural settings in the Netherlands. Of note, the trial excludes anyone over 50 years of age , which may limit generalisability to many other countries, including Australia where the median age for ECPR is over 60 year old. Data for the Australian context is urgently needed. A further imperative to complete this trial is that ECPR systems are expensive and resource intensive, so there must be compelling evidence that it saves a sufficient number of lives with excellent neurological recovery before there is widespread adoption of this treatment into practice in Australia and globally. Our research team recently surveyed 130 critical care clinicians from around Australia, and 105 (81%) of respondents said research into cost effective strategies for ECPR was a high priority.

6. OBJECTIVES

6.1 Aim

To determine whether a prehospital ECPR strategy is associated with improve hospital survival in patients with refractory OHCA, as compared with a conventional cardiac arrest strategy, including salvage hospital based ECPR.

6.2 Hypothesis

Prehospital ECPR is associated with an increased hospital survival in patients with refractory OHCA, as compared with standard care.

7. OVERALL STUDY DESIGN

7.1 Study design

This is a target trial emulation designed to compare the outcomes of a prehospital ECPR strategy with a conventional cardiac arrest strategy for patients with refractory OHCA. The study will use observational data from pre-existing registries to simulate a RCT. Advanced statistical methods will be employed to control for confounding variables.

7.2 Inclusion Criteria

1. Adult patients 18-70 years old
2. Witnessed cardiac arrest
3. Bystander CPR
4. Refractory cardiac arrest (defined by failure to achieve sustained ROSC >20 mins post initiation of CPR)
5. Initial cardiac rhythm VF, VT or PEA
6. Within the hours of prehospital ECPR service operation (i.e. Monday to Friday 0900-1700)

7.3 Exclusion Criteria

1. Initial cardiac rhythm asystole, traumatic cardiac arrest
2. ROSC with sustained recovery
3. Unable to reach the patient and commence cannulation within 45 minutes of onset of arrest
4. Evidence of/suspected end stage disease:
    - Severe disability impairing activities of daily living
    - End-stage organ – cardiac, liver, lung, renal
    - Other life-limiting diseases e.g. malignancy, terminal illness

- Advance health care directive (not for resuscitation)

5. Time periods of advanced public health restrictions in Victoria or NSW due to COVID-19.

7.4 Data Registries

7.4.1 EXCEL Data Registry

The EXCEL Registry is a comprehensive, national registry which captures admission, in-hospital and long-term outcome data of patients requiring ECMO (HREC 43134).

7.4.2 The CHEER 3 Study

The CHEER 3 study is an observational study of prehospital ECPR for refractory OHCA in metropolitan Melbourne (HREC 46089). The recruitment period commenced in 2019 and is ongoing. Participants enrolled during COVID-19 imposed lock-down periods will not be included due to a reduction in survival for all cardiac arrests during that period.

7.4.3 The PRECARE Study

The PRECARE study is an observational study of prehospital ECPR for refractory OHCA in greater Sydney (HREC X23-0150 2023/ETH00767). The study commenced recruitment August 2023 recruitment is ongoing.

7.4.4 The Victorian Ambulance Cardiac Arrest Registry (VACAR)

VACAR is a quality assurance initiative. It captures data on all out-of-hospital cardiac arrests attended by emergency medical services in Victoria. The registry commenced in October 1999.

7.4.5 The Evidence Study Registry

The EVIDENCE study (Expedited intra-arrest transport versus more extended on-scene resuscitation for refractory out of hospital cardiac arrest HREC (2021/ETH00318), was a prospective randomised control trial which recruited from July 2021 to March 2024. The inclusion criteria into this study closely mirrors that of the CHEER 4 study, aged 18-70, witnessed arrest, bystander CPR, VT/VF/PEA and no return of spontaneous circulation after 15 minutes or 3 rounds of professional. EVIDENCE compared conventional resuscitation strategies. This study includes at RCT (n=197) and a registry arm, which prospectively captured patients not enrolled in the RCT for any reason. The data of appropriate patients from both RCT and registry arm of the EVIDENCE study will be made available for comparator group for the CHEER 4 TTE and agreement from the steering committee is attached.

7.4.6 The NSW Ambulance OHCA Registry Data Linkage Project

NSWCAR is a clinical quality initiative. The registry contains cases attended by NSW Ambulance clinicians starting from 1 January 2017.

7.5. Study Population

The study population include patients with OHCA in the metropolitan Melbourne region and greater Sydney metropolitan region, who meet all of the inclusion and none of the exclusion criteria.

7.6. Interventions

7.6.1. Prehospital ECPR Strategy (Intervention Cohort)

Two feasibility studies assessing prehospital ECPR have been running concurrently in NSW (The PRECARE Study) and Victoria (The CHEER 3 Study). Patients enrolled in these trials will be screened for the CHEER 4 TTE inclusion and exclusion criteria and will form the Intervention cohort. Data for these patients will be obtained from the PRECARE Study and CHEER 3 Study data sets and EXCEL registry.

The intervention being tested is prehospital ECPR for refractory OHCA. Refractory OHCA is diagnosed when prolonged resuscitation >20 minutes fails to achieve sustained ROSC. All calls to EMS for OHCA are preliminarily screened for prehospital ECPR criteria. The ECPR clinical team attend preliminarily eligible patients within a geographical region of no more than 45 minutes travel time from the prehospital ECPR service. Upon their arrival, the patient is formally screened for the inclusion and exclusion criteria. If eligible,

and refractory cardiac arrest is diagnosed and there is still no ROSC the patient is assigned to the prehospital ECPR strategy.

The specialist ECPR clinicians commence the ECPR process. The patient is intubated and mechanically ventilated and mCPR is commenced, if not already done prior to ECPR clinical team arrival. Ultrasound guided femoral-femoral VA ECMO cannulation is performed by the prehospital ECPR team. Canulae are connected to a portable ECMO pump and chest compressions are discontinued when VAECMO blood flow is greater than 3.0L/min.

Prehospital notification is given to the coronary catheterisation laboratory of the ECMO specialist hospital. The patient is then extricated from the scene and transported to the Emergency Department of the ECMO specialist hospital for ongoing post cardiac arrest investigations and management.

All treatment beyond the initiation of prehospital ECPR is in line with standard care.

7.6.2 Conventional Cardiac Arrest Strategy (Control Cohort)

The control cohort will be identified from existing OHCA registries:

- VACAR
- The EVIDENCE study data set
- The NSW Ambulance OHCA Registry Data Linkage Project

These data sets will be screened for the CHEER 4 TTE inclusion and exclusion criteria. Those patients who meet all inclusion and no exclusion criteria and *DID NOT receive prehospital ECPR* will be included in the Control cohort.

Intervention patients co-enrolled in CHEER 3 (Victoria) will be matched with patients identified within the VACAR registry within the same time window in which the CHEER 3 study was recruiting.

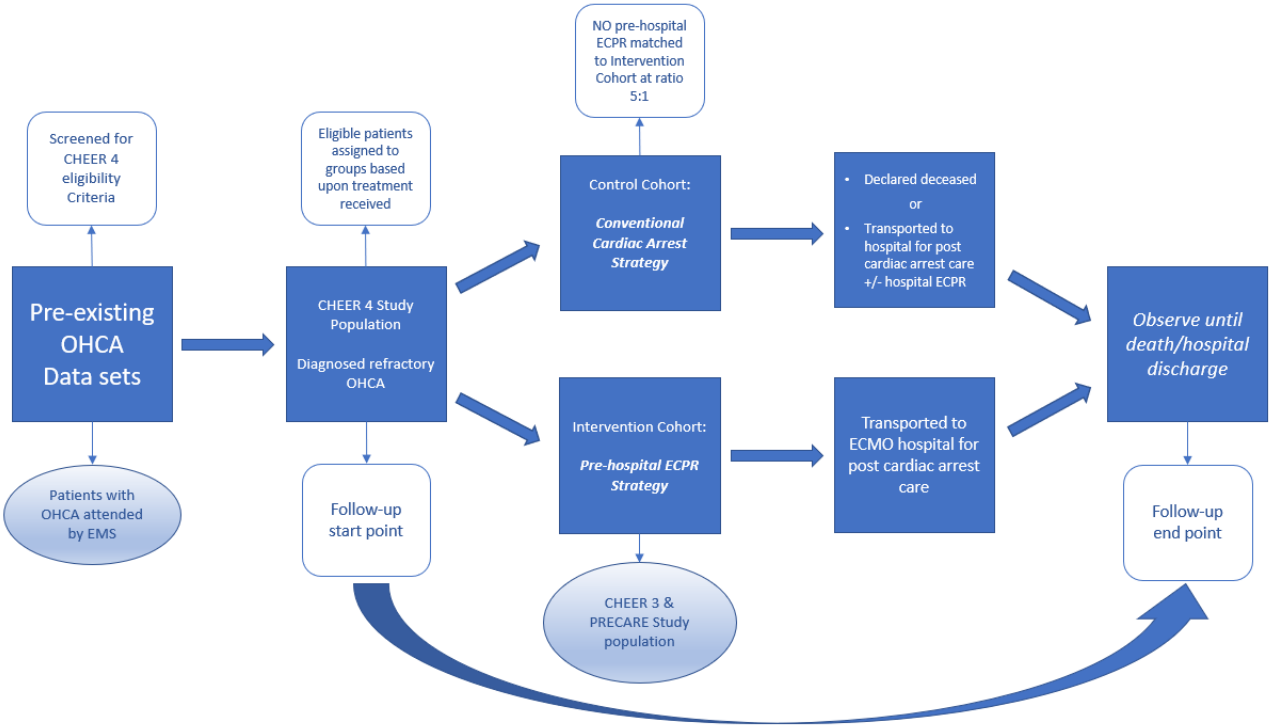
Intervention patients co-enrolled in PRECARE (NSW) will be matched with patients identified within the EVIDENCE study /NSW Ambulance OHCA Registry Data Linkage Project.

Patients included during COVID-19 related lock-down periods will not be included in the CHEER 4 control cohort due to reduced survival for conventional resuscitation noted during this period.

The control group includes patients with refractory OHCA that are NOT attended by the prehospital ECPR service. The respective datasets will be screened for patients within a geographical region no more than 45 minutes travel time from the prehospital ECPR service (matching regions to the intervention cohort). At the time that refractory OHCA is diagnosed (>20 minutes post OHCA), the patient is assigned to the control cohort. This time point serves as a surrogate for the time of randomisation (matching the intervention cohort).

The treatment strategy is the continuation of conventional cardiac arrest care, which may include declaring the patient deceased at the scene or commencing mCPR and transporting the patient to the nearest percutaneous coronary intervention (PCI) capable hospital for ongoing investigations and management with +/- hospital based ECPR.

7.7 CHEER 4 TTE Flow chart



8. STUDY OUTCOME MEASURES

8.1 Primary Outcome

Survival to hospital discharge

8.2 Secondary Outcomes

1. Low flow time (time from arrest to ECPR flow or ROSC)
2. ICU length of stay
3. Mechanical ventilation days
4. The number of patients with a cerebral performance category (CPC) of 1 or 2 at hospital discharge
5. Rates of organ and tissue donation in non-survivors
6. ECMO complications, including major bleeding episodes and blood culture positive sepsis
7. Long term outcomes, including 6 and or 12-month survival and quality of life

9. CONSENT AND ETHICAL CONSIDERATIONS

9.1 Ethical conduct of the trial

This study will be performed in accordance with all relevant ethical and regulatory approvals and guidelines laid down by the National Health and Medical Research Council of Australia, the Declaration of Helsinki, its subsequent amendments, and the ICH-GCP guidelines on the ethical conduct of research. This study is approved by the Alfred Hospital Ethics Committee (103811). Research Ethics approval will be obtained prior to the start of the study and HREC documents will be approved by the Research Governance Office at each institution.

9.2 Waiver of consent

Enrolment will be subject to a waiver of consent. This research is observational and there is no intervention. Inclusion in the study carries no more risk than low risk. The data being collected for CHEER 4 TTE will be obtained retrospectively from pre-existing OHCA data sets making it impracticable to obtain consent for this research. All data sets from where data will be obtained (see section 7.4) have undergone review by a Human Research Ethics Committee (HREC) which granted a waiver for consent and approval for data collection in compliance with ethical guidelines.

The aim of this study is to determine whether the treatment strategy may improve the outcomes for a group of otherwise healthy patients faced with little chance of survival to hospital discharge. The potential benefits from this research justify any risk of harm associated with not seeking consent.

All data transferred to Monash will be anonymised and stored on a secure server. Any publications will be of grouped anonymised data with no individual data being reported.

This process is in line with the National Statement 2.3.10 as follows:

> ***a) involvement in the research carries no more that low risk to participants:***
> This is a low risk project; it is observational and there is no-intervention. All data being collected for the study has been routinely collected by HREC approved quality assurance registries or research projects. Participation requires no additional action on the part of the patient or families.
>
> ***b) the benefits from the research justify any risks of harm associated with not seeking consent:***
> As mentioned above, this is a low risk project. Patients with refractory cardiac arrest have a hospital survival rate of approximately 2%. ECMO has the potential to save lives and increase survival rates for this group of patients. This research aims to generate valuable insight about pre-hospital ECPR that will benefit future clinical practice and future research, with potential to improve patient outcomes for a group of patients who would otherwise likely die.
>
> ***c) it is impracticable to obtain consent (for example, due to the quantity, age or accessibility of records):***
> Patients included in this project are being identified retrospectively, making it impracticable to obtain consent. With current survival rates following OHCA at approximately 10%, the vast majority of patients to be included in this research will be deceased. Seeking consent from grieving families to use data has already been collected for the purpose of similar research could impose an unnecessary burden and distress.
>
> ***d) there is no known or likely reason for thinking that participants would not have consented:***
> Patients included in the intervention cohort of CHEER4 TTE will be identified within the CHEER 3 and PRECARE study data sets. Survivors or their person responsible (PR), were informed of their inclusion in these studies by an Investigator during their hospital admission. The family of non-survivors have been notified of their loved one's inclusion into PRECARE or CHEER 3 by way of a condolence letter. The Chief Investigator for each of these studies has informed us that no patient or their PR have indicated that they do not wish to be included in PRECARE or CHEER 3. If there were to be patients who indicated that inclusion in research was not in keeping with their wishes,

we would not include their data in our analysis. In addition, in our experience families are usually quite willing to be involved in research that could help people going through similar circumstances.

e) there is sufficient protection of their privacy:
Strict data management and governance guidelines will be drafted to ensure the privacy and confidentiality of all study information. This will include ensuring that the data are stored securely on a Monash University server which is compliant with all State and National requirements.

f) there is an adequate plan to protect the confidentiality of data:
Only re-identifiable data will be sent to the coordinating site. Any publications that arise from this research will only use aggregate data, there will be no reference to individual patients.

g) in case the results have significance for the participants' welfare there is, where practicable, a plan for making information arising from the research available to them (for example, via a disease-specific website or regional news media):
There will be no direct benefit to the patients included in this project, rather the results will be directly relevant to society in general and future patients with OHCA. However, the results of this project might be disseminated via radio and TV interviews, news articles etc. Our group has extensive experience in sharing their research findings to the broader community.

h) the possibility of commercial exploitation of derivatives of the data or tissue will not deprive the participants of any financial benefits to which they would be entitled:
There will be no monetary financial benefits and there will be no possibility of commercial exploitation.

***i) the waiver is not prohibited by State, federal, or international law*:**
Waiver of consent is allowed in the participating states - Victoria and NSW.

9.3 Data protection and participant confidentiality

Confidentiality of all patient data will be maintained by the use of unique identifiers, passworded electronic databases, secure storage of records and precautions taken to control access. All records will be kept in compliance with local ethical and research governance policies.

10. DATA MANAGEMENT

10.1 Data collection methods and retention period

All data for the CHEER 4 TTE study will be obtained from pre-existing data sets (see section 7.4 of this protocol).

Data will be transferred to Monash University using Monash University's Secure File Transfer Protocols (SFTP). These controls are regularly externally audited to ensure they meet global best practices and are aligned with ISO 27001 security practices. Data collected will be stored on University managed secure and resilient infrastructure located in Australia that complies with all applicable data protection and privacy legislation.

Data will be retained by Monash University for a period of 15 years post completion of the study in keeping with the university requirements. After this time point all data will be destroyed.

The use of any data collected for this study will be at the discretion of the investigators and all will be limited to the aims of the CHEER 4 TTE study. Any requests for use of the CHEER 4 TTE dataset may firstly require approval from the initial collection source.

10.2 Data Variables Collected

Baseline Demographic data

- age, sex, hospital admission diagnosis, comorbidities

Cardiac Arrest specific data:

- OHCA Date/time
- Initial recorded rhythm
- Date/time of refractory OHCA >20 mins failure to achieve ROSC
- Date/time of any ROSC
- Date/time of prehospital ECPR
- No Flow duration
- Low Flow duration

Hospital Outcomes:

- Hospital based ECMO
- ICU discharge
- Hospital Discharge
- ECMO duration
- ECMO complications
- Hospital Mortality
- Organ donation
- Mechanical Ventilation duration

10.3 Data monitoring

Data monitoring will not be routine as all data is being sourced from pre-existing data-sets with data-monitoring plans in place. However manual verification will be sort from the respective data custodian for any extreme data values.

11. STATISTICAL CONSIDERATIONS

11.1 Sample size calculation

Based on current recruitment in the CHEER 3 and PRECARE studies, we propose to collect data on approximately 50 patients in the prehospital ECPR group by the end of 2024. The conventional cardiac arrest management group sample size will be determined by including all eligible patients over the same period of time that the CHEER 3 and PRECARE studies were operational (2019-2024). We anticipate this group will be significantly larger (circa 250 patients) than the prehospital ECPR group given the relatively small number of hours of operation of the prehospital ECPR services have been available during this period of time.

11.2 Statistical analysis plan

A detailed statistical analysis plan will be developed and published separately from this protocol. This plan defines the full analysis set, accompanied by an analysis seeking to estimate the average causal effect. It outlines the specific features of the target trial emulation which are used to “simulate” a randomised control trial setting. The per-protocol effect under full adherence will be estimated using the parametric g-formula and/or marginal structural models with inverse probability weighting.

Data analysis will be performed independently by a statistician who is blinded to the allocated intervention arms, with reporting of results according to the CONSORT statement.

12. SAFETY – ADVERSE EVENTS

All data is being obtained from pre-existing data sources. Any serious adverse events observed in the data that may be related to the intervention will be reported to the Management Committee and the HREC.

13. CONSUMER ENGAGEMENT

Consumer representatives are part of the management committee for the national EXCEL registry, which serves as the source for all ECMO-related data, including outcomes for OHCA patients supported by VA-ECMO. Given the consistently poor outcomes for OHCA, this remains a critical area for future research.

14. AUTHORSHIP AND PUBLICATION

The study will be conducted in the name of the CHEER 4 TTE investigators and the ANZIC-RC. The central project coordination and data management will be provided by the ANZIC-RC at Monash University, Melbourne. The principal publication from the study will be in the name of the CHEER 4 TTE Investigators with full credit assigned to all collaborating investigators and institutions. Where individual names are required for publication, these will be that of the writing committee, with the chair of the writing committee listed first and subsequent authors listed alphabetically.

15. RESEARCH TIMELINES

Time frame indicators	Milestone
Develop Protocol and Ethics	November 2024
Commence screening for recruitment	February 2025
Data Analysis	March 2025
Manuscript completed	May 2025

16. FUNDING

The CHEER 4 TTE trial is funded by project grants from the Heart Foundation (Vanguard Grant: 107045). The ANZIC-RC will supply infrastructure and administrative support.

17. TRIAL REGISTRATION

This trial will be registered on a Clinical Trials Registry Platform.

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19. APPENDICES

Appendix 1: Summary of the Protocol of the Target Trial Assessing the effect of pre-hospital ECPR for OHCA on hospital survival

Components	Hypothetical randomised trial	Emulation
Eligibility	Adult patients with refractory OHCA entered into OHCA registries in NSW in Victoria ***Inclusion Criteria:*** 1. Adult patients with18-70 years old 2. Witnessed cardiac arrest 3. Bystander CPR Refractory cardiac arrest (defined by failure to achieve sustained ROSC by >20 minutes post initiation of CPR) 4. Initial cardiac rhythm VF, VT or PEA 5. Within the hours of pre-hospital ECPR service operation 6. Ability to reach the patient and commence cannulation within 45 minutes of onset of arrest ***Exclusion Criteria:*** 1. Initial cardiac rhythm asystole 2. ROSC with sustained recovery 3. Evidence of/suspected end stage disease: • Severe disability impacting activities of daily living • End-stage organ disease – cardiac, liver, lung, renal • Other life-limiting diseases (eg. malignancy, terminal illness) • Advance health care directive (not for resuscitation) 4. Time periods of advanced public health restrictions in Victoria and NSW due to COVID 19	Same as hypothetical
Treatment strategies	• Pre-hospital ECPR Strategy • Conventional Cardiac Arrest Strategy	Same as hypothetical

Treatment assignment	At 20 minutes of CPR without sustained ROSC, patients are assigned to one of two strategies. Stratification was performed based on: • Age • duration of cardiac arrest • presence of any ROSC • and state The treatment team was aware of the assigned treatment strategy.	Assumed that patients were randomly assigned within levels of the following baseline variables: • CPR Duration • Any ROSC • Location • Site
Follow-up	The follow-up started at the time of assignment to a treatment strategy and ended at either: • Death, or • Discharge from Hospital (competing event)	Same as hypothetical
Causal contrast	Per protocol effect	Observational analogue of the per protocol effect
Statistical analysis	In the per-protocol analysis, patients were censored when they deviated from their assigned strategy. The per-protocol effect was estimated after adjustment for baseline variables and for time-varying variables associated with adherence to the strategy	Same as hypothetical trial. The per-protocol effect under full adherence was estimated using the parametric g-formula. The value of each density function for all possible covariate histories was estimated under parametric modelling assumptions. The approximated sum over all histories was subsequently calculated via Monte Carlo simulation. The per-protocol effect was also estimated using a different methodological approach based on marginal structural models with inverse probability weighting