



Blend to Limit oxygEN in ECMO:
a ranDomised controllEd Registry trial
The BLENDER Trial –
A Phase II Multicentre Randomised Controlled Trial

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Endorsements:	Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS-CTG): CTG1819-05 Endorsed by the International ECMO Network (ECMONet)

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1. GLOSSARY OF ABBREVIATIONS AND TERMS

AE	Adverse event
ANZIC-RC	Australian and New Zealand Intensive Care Research Centre
ANZICS CTG	Australian and New Zealand Intensive Care Society Clinical Trials Group
ANZICS CORE	Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation
APD	Adult Patient Database
ARDS	Adult Respiratory Distress Syndrome
CRF	Case Report Form
DSMC	Data and Safety Monitoring Committee
ECMO	Extracorporeal Membrane Oxygenation
ECMOnet	International Extracorporeal Membrane Oxygenation Network
eCRF	Electronic Case Report Form
ELSO	Extracorporeal Life Support Association
EQ5D5L	European Quality of Life 5 Dimensions 5 Level
EXCEL	A comprehensive national registry on the treatment and outcomes of patients requiring ECMO
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HRC	Health Research Council
HREC	Human Research Ethics Committee
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IMV	Invasive Mechanical Ventilation
LCTRC	Lifting Clinical Trials and Registries Capacity
NHMRC	National Health and Medical Research Council
MRFF	Medical Research Future Fund
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
RGO	Research Governance Officer
SAE	Serious Adverse Event
SD	Standard Deviation
SDM	Substitute Decision Maker
SPIRIT	Standard Protocol Items: Recommendation for Interventional Trials
V-A	Veno-Arterial
V-V	Veno-Venous
WHODAS	World Health Organisation Disability Assessment Schedule 2.0

2. SYNOPSIS

Title	Blend to limit oxygen in ECMO: A randomised controlled registry trial
Short Title	The BLENDER trial
Objective	To determine in patients requiring venoarterial (V-A) ECMO, whether the use of a conservative as compared with liberal oxygen strategy, results in a greater number of alive and ICU-free days at day 60.
Hypothesis	In patients receiving V-A ECMO, a conservative compared to liberal oxygen strategy increases the number of alive and ICU-free days at day 60.
Design	This is a phase II, registry-based, multicentre, parallel group randomised controlled trial.
Sample Size	300 patients
Sites	Up to sixteen ECMO centres in Australia and New Zealand. Australian sites include: The Alfred Hospital, The Prince Charles Hospital, Royal Prince Alfred Hospital, St Vincent's Hospital (Sydney), Royal Melbourne Hospital, Fiona Stanley Hospital, The Austin Hospital, Geelong University Hospital, Monash Medical Centre, The Royal Adelaide Hospital, Flinders Medical Centre, Gold Coast hospital, Princess Alexandra Hospital, The Royal North Shore Hospital, Box Hill Hospital and New Zealand sites - Auckland City Hospital.
Population	Adult patients requiring V-A ECMO
Eligibility Criteria	<i>Inclusion Criteria:</i> Patients ≥18 years who are commenced on V-A ECMO for severe cardiac, or following refractory cardiac arrest. <i>Exclusion Criteria:</i> - Greater than six hours have elapsed from the time of initiation of ECMO to randomisation - Patients who are suspected or confirmed to be pregnant - Where an indication exists for a specific oxygen target as part of clinical care (e.g. CO poisoning) - The patient is already enrolled in another oxygen titration study - Patients not willing to receive blood products (e.g. Jehovah's Witness) - Where the treating physician deems the study is not in the patient's best interest
Strategies	Each eligible and enrolled participant will be randomised to either a conservative or liberal oxygen strategy while receiving V-A ECMO during the period from randomisation up to day 60. <i>Conservative Strategy</i> Patients allocated to the conservative strategy will have the ECMO blender oxygen fraction (FbO₂) titrated to achieve a post-oxygenator saturations of 92-96% (the FbO₂ cannot be reduced to lower than 0.5). Post-oxygenator arterial blood gases (ABG's) will be taken to ensure safety and to allow for adjustments to be made. The ventilator Fio₂ will initially be titrated to patient oxygen saturations (SpO₂) of 92-96%.

	<i>Liberal Strategy</i> Patients allocated to the liberal strategy will have the FbO₂ set at 1.0 at all times. The ventilator FiO₂ will initially be set at 0.6, and then titrated to achieve a patient oxygen saturations (SpO₂) of 97-100%. If patient oxygen saturations (SpO₂) remain between 97-100% clinicians are advised to reduce FiO₂ on the ventilator to a minimum of 0.5.
Outcomes	<i>Primary outcome</i> The primary outcome for this study is the number of days alive and free of ICU at day 60. <i>Secondary outcomes</i> 1. Number of alive and ICU-free days at day 60 (accounting for exit block) 2. Hospital mortality 3. ICU mortality 4. Hospital length of stay 5. ICU length of stay 6. Duration of mechanical ventilation 7. Six and twelve month mortality 8. Disability at six and twelve months measured with the World Health Organisation's Disability Assessment Schedule 2.0 12L 9. Quality of life measured at six and twelve months with the EQ5D-5L 10. Neurocognitive function assessed at six and twelve months with the Montreal Cognitive Outcomes Assessment and the Glasgow Coma Scale Extended. 11. Functional ability at six and twelve months with Instrumental Activities of Daily Living (IADL) <i>Tertiary Outcomes</i> 1. ECMO circuit life 2. Cost effectiveness
Study Duration	All enrolled patients will be followed to twelve months post-randomisation date or to death if death occurs within that twelve month timeframe. Recruitment is expected to take ~5 years, starting in 2019.

3. STUDY ADMINISTRATION STRUCTURE

3.1 Coordinating Centre and Data Management Centre in Australia

Australian and New Zealand Intensive Care Research Centre (ANZIC-RC)
School of Public Health and Preventive Medicine, Monash University
553 St Kilda Road, Melbourne, Victoria, 3004 AUSTRALIA
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Responsibilities:

- Overall management of the trial including assistance with human research ethics committee applications
- Management of study budget and liaison with funding bodies
- Protocol and case report form (CRF) design and production
- Database design and management
- Protocol training of investigators, research coordinators and clinicians
- Preparation and arrangement of investigator payments
- Trial set-up
- Randomisation
- Coordination of data entry and feedback of data enquiries
- Monitoring and close-out site visits
- Organisation of investigator meetings
- Serious adverse event notification
- Data analysis and collaboration on publications

3.2 Management Committee Responsibilities

Overseeing all aspects of the study management including:

- Liaison with coordinating centre staff and trial management centre staff
- Liaison with ANZICS-CTG and/or the ECMO-Net
- Overseeing funding applications
- Overseeing disbursement and administration of funds
- Ensuring fiscal responsibilities are maintained
- Development and approval of final protocol and trial materials
- Development and approval of data collection tools and methods
- General trial management issues

3.3 Steering Committee

Name	Role	Institution
Dr Aidan Burrell	Intensivist	Alfred Health
A/Professor David Gattas	Senior Intensive Care Specialist	Royal Prince Alfred Hospital
Professor Carol Hodgson	Deputy Director	ANZIC-RC, Monash University
Ms Kelly Ottosen	BLENDER Project Manager	ANZIC-RC, Monash University
Professor David Pilcher	Senior Intensive Care Specialist	Alfred Health
Mr Tony Trapani	Research Manager	ANZIC-RC, Monash University
Professor Andrew Udy	Deputy Director	ANZIC-RC, Monash University

3.4 Role of the Funders

This is an investigator-initiated study. The management committee will take responsibility for study design and oversight. The funders will have no role in study design, data collection, management, analysis, data interpretation, manuscript writing, or in the decision to submit manuscripts for publication.

3.5 Project Manager

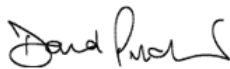
Management Committee Chair	Project Manager
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4. MANAGEMENT COMMITTEE AUTHORISATION PAGE

We, the management committee, have read the attached protocol and authorise it as the official protocol for the study entitled: Blend to limit oxygen in ECMO: a randomised controlled registry trial: A Phase II Multicentre Randomised Controlled Trial (BLENDER).

Chief Investigator

Prof David Pilcher



Date:

04/02/2019

Management Committee

Prof Michael Bailey



Date:

04/02/2019

Management Committee

Prof Rinaldo Bellomo



Date:

06/02/2019

Management Committee

Dr Aidan Burrell



Date:

04/02/2019

Management Committee

Dr Hergen Buscher



Date:

05/02/2019

Management Committee

Ms Amanda Corley

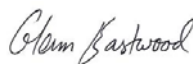


Date:

17/05/2019

Management Committee

Dr Glenn Eastwood

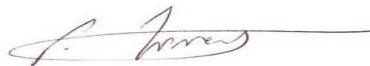


Date:

04/02/2019

Management Committee

Dr Paul Forrest

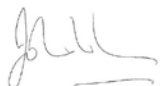


Date:

05/02/2019

Management Committee

Prof John Fraser



Date:

06/02/2019

Management Committee

A/Prof David Gattas



Date:

06/02/2019

Management Committee

Prof Carol Hodgson



Date:

04/02/2019

Management Committee

Ms Alisa Higgins



Date:

04/02/2019

Management Committee

A/Prof Andrew Hilton



Date:

06/02/2019

Management Committee

Dr Edward Litton



Date:

04/02/2019

Management Committee

A/Prof Chris MacIsaac



Date:

04/02/2019

Management Committee

Ms Emma Martin



Date:

15/04/2019

Management Committee

Dr Priya Nair



Date:

04/02/2019

Management Committee

A/Prof Neil Orford



Date:

04/02/2019

Management Committee

Ms Kelly Ottosen



Date:

28/08/2019

Management Committee

A/Prof Vincent Pellegrino



Date:

06/02/2019

Management Committee

Ms Liadain Reid



Date:

05/02/2019

Management Committee

A/Prof Kiran Shekar



Date:

04/02/2019

Management Committee

Mr Tony Trapani



Date:

06/02/2019

Management Committee

Prof Andrew Udy



Date:

04/02/2019

Management Committee

Dr Marc Ziegenfuss



Date:

17/07/2019

5. LAY DESCRIPTION

Extracorporeal membrane oxygenation (ECMO) can be a lifesaving procedure for the sickest patients in the Intensive Care Unit (ICU) who are at risk of death from severe cardiac and respiratory failure. ECMO is a device which pumps blood out of the body and returns it back after adding oxygen and removing carbon dioxide. While potentially life-saving, ECMO is associated with high use of critical care resources and increased risk of adverse outcomes in survivors.

The BLENDER Trial is a multicentre trial in ECMO patients to determine whether a conservative oxygen strategy during ECMO reduces ICU length of stay and improves patient outcomes compared to a liberal oxygen strategy. Both strategies are currently standard practice worldwide, however, there is no consensus to which strategy is better for our patients. This trial aims to utilise an existing intensive care registry and will recruit 300 patients with life threatening acute cardiac or respiratory failure. If the BLENDER Trial confirms that one oxygen management strategy is more effective than the other, its findings may improve the lives of critically ill Australians and inform clinical practice worldwide.

6. ADMINISTRATIVE INFORMATION

6.1 Funding

This study is funded by a research grant from the Medical Research Future Fund (MRFF) – Project Grant ID GNT1152270.

6.2 Trial Registration

This protocol has been registered on the following registry:
Clinicaltrials.gov: ID NCT03841084

7. BACKGROUND AND SIGNIFICANCE

7.1 Key Concepts

- The use of ECMO in Australia has increased despite high costs and adverse outcomes.
- Both conservative and liberal oxygen strategy are in use worldwide and equipoise exists among clinicians.
- Preliminary work shows that a conservative oxygen strategy may improve outcomes.
- Collection of data on patients will occur almost exclusively through pre-existing registries (EXCEL registry for in-depth daily data about ECMO provision, complications and long-term outcomes; ANZICS Adult Patient Database for baseline ICU demographics, severity of illness and in-hospital mortality outcomes; ANZICS-ECMO registry for baseline severity of illness markers and basic ECMO complications).
- The only information that will require dedicated data collection will be randomisation, protocol deviations and serious adverse events specific to the BLENDER trial.
- A multicentre definitive study to establish efficacy in ECMO patients is now needed to test whether a conservative oxygen strategy can improve outcomes.
- Our trial design will allow us to test our hypothesis with sufficient power and rigour.
- Whichever strategy is proven to improve outcomes in our sickest and most resource intensive ICU patient group will become the standard of care.
- This trial will be conducted by researchers with extensive expertise in large registries and clinical trials and will be immediately translatable through clinical trials groups and education.

7.2 Severe Heart Failure Treated by ECMO has Extremely High Mortality

Patients suffering severe cardiac and respiratory failure requiring intensive care have extremely high mortality and morbidity, and impose significant financial costs to society. ECMO is a mechanical life support device that may offer improved outcomes for a highly selected subgroup.¹ However, even in the best centres, ECMO is associated with a high mortality rate (30-50%) and prolonged multiple organ (especially cardiac, pulmonary, and cerebral) failure.² The configuration of ECMO used for cardiac failure differs from that used for respiratory failure. In both configurations, transfer of oxygen and carbon dioxide occurs across a membrane, which separates blood from the fresh gas flow.

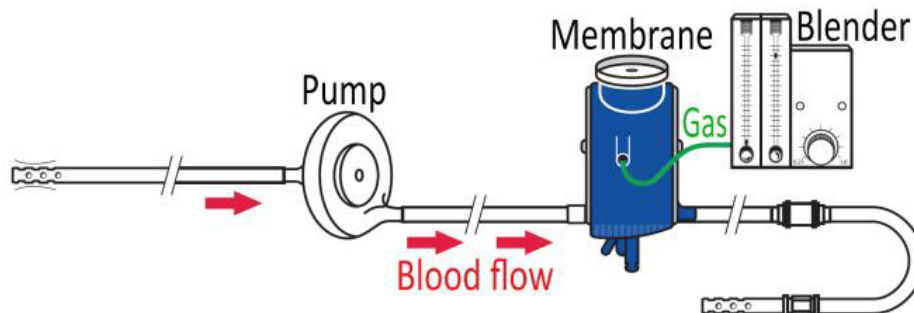


Figure 1: ECMO circuit with Oxygen Blender

Veno-arterial ECMO (V-A ECMO) is used for patients with refractory cardiac failure or refractory cardiac arrest, and restores perfusion of oxygenated blood to the body, allowing time for recovery or assessment for permanent mechanical artificial heart support. V-A ECMO drains venous blood, removes carbon dioxide and returns oxygenated blood to the arterial system in quantities sufficient to provide complete circulatory support.

In ECMO patients, the fraction of oxygen in the fresh gas delivered to the membrane (FbO_2) was traditionally maintained at 1.0 (or 100% O_2), however, in recent years a significant number of centres (within Australia and worldwide) are now titrating the FbO_2 according to patients' needs. While, 100% O_2 is frequently used in order to prevent low oxygen levels in the patient (hypoxia), this more commonly results in abnormally high levels of oxygen in the blood (hyperoxia).

In the BLENDER trial, we will determine whether a conservative oxygen strategy [achieved by targeting lower peripheral oxygen saturations (SpO_2), and reduced fractions of oxygen delivered to the ECMO membrane (FbO_2), and the lung (FiO_2)], improves outcomes in critically ill patients receiving V-A ECMO, as compared to a liberal oxygen strategy.

7.3 Hyperoxia is Common in Patients on ECMO

The typical approach to oxygen management in ECMO (where high FbO_2 values are applied) frequently results in hyperoxia. In a recent study of 1942 ECMO patients from the Extracorporeal Life Support Organization (ELSO) Registry, the median partial arterial pressure of oxygen (PaO_2) at 24 hours was 180mmHg when V-A ECMO was used for cardiogenic shock, 195mmHg when used post-refractory cardiac arrest, and 94mmHg for V-V ECMO.³ Fifteen per cent of non-cardiac arrest V-A ECMO cases, and 22% of those receiving V-A ECMO post-refractory cardiac arrest, had severe hyperoxia ($PaO_2 > 300$ mmHg).³

In unpublished pilot data from The Alfred Hospital, oxygen tensions in 40 patients post-cardiac arrest were compared between those that did ($n=20$) and did not ($n=20$) receive V-A ECMO. Median PaO_2 values were significantly higher in the V-A ECMO group (436 vs. 148mmHg $p<0.001$), and remained so for the first 72 hours ($p<0.01$). In a second pilot study of 39 ECMO patients admitted to The Alfred Hospital from January to September 2017, mean post-membrane oxygen tensions in the first 3 days were 495mmHg (SD ± 115), and remained elevated on days 3-7 [mean PaO_2 of 478mmHg (SD ± 99)].

7.4 Rationale for a Conservative Oxygen Strategy

Animal studies have shown that hyperoxia increases free radical production, worsens ischaemia reperfusion injury, and induces inflammatory damage. In humans, hyperoxia results in significant lung collapse, alveolar leak, and fibrotic changes.⁴ Hyperoxia can induce cerebral and coronary vasoconstriction, which can worsen ischaemic injuries.^{5,6} In addition, several recent systematic reviews have demonstrated an association between hyperoxia and increased mortality in cardiac arrest, traumatic brain injury, stroke, and hospitalized patients.^{7,8} There is also a growing body of data suggesting that ECMO patients may be especially vulnerable to oxygen toxicity. ECMO typically results in very high PaO₂ values, generating significant oxidative stress and inflammation⁹, in addition to platelet dysfunction, which can lead to thrombosis¹⁰. In a recent study examining PaO₂ values in ECMO patients at 24-hours, moderate hyperoxia (PaO₂ 150-300mmHg) was associated with increased mortality in patients receiving V-A ECMO for refractory cardiac arrest (OR 1.77; 95% CI, 1.03–3.30).³

7.5 Evidence that Reducing Oxygen may be Beneficial

There is growing evidence that a conservative oxygen strategy (manifest as lower SpO₂ targets and reduced FiO₂ values) in critically ill patients not receiving ECMO, results in improved patient outcomes. The AVOID trial demonstrated a reduction in infarct size with a strategy of air rather than oxygen in patients presenting with acute myocardial infarction.¹¹ In the HYPERESS2 RCT the incidence of atelectasis and weakness were reduced with a conservative SpO₂ target (88-95%).¹² Finally, Girardis et al. found a reduction in organ failures and mortality in their RCT of conservative (SpO₂ 94-98%) versus liberal (SpO₂ 97-100%) oxygen targets in ventilated critically ill patients.¹³

Our research team recently completed a survey of 35 critical care clinicians from seven major ECMO centres in Australia. Eighty-nine per cent of respondents were concerned about oxygen toxicity in their ECMO patients, with over twenty per cent titrating the FbO₂ routinely.

7.6 BLENDER Trial Significance and Knowledge Translation

Current ECMO guidelines do not specify an optimal oxygen strategy. Practice variation currently exists and there are clinical concerns regarding avoidable supra-normal oxygen levels.² In the absence of clinical trials in this area, there is a clear knowledge gap. Improving outcomes in ECMO patients may have high cost benefits. ECMO is experiencing a rapid growth in clinical use globally, so although a rare device for rare patient conditions, the costs and resource implications are significant (~AU\$50M is spent annually on this therapy). Moreover, ECMO patients remain in hospital for long periods, and survivors face long periods of recovery.

The BLENDER Trial aims to test a simple intervention that may significantly improve the care provided to ECMO patients, in addition to potentially reducing health-care costs. Importantly, the intervention can be rapidly commenced in experienced Australian ECMO centres, without additional equipment. These data will significantly influence clinical practice globally. Finally our linkage with established clinical registries (ANZICS-APD, EXCEL) means the trial will be conducted efficiently, and with the minimum expenditure.

8. STUDY OBJECTIVES

To determine in patients undergoing V-A ECMO, whether the use of a conservative oxygen strategy, as compared to liberal oxygen strategy, will result in a greater number of ICU free days at day 60. Other outcomes including the effect on ECMO and mechanical ventilation duration, circuit life, hospital mortality, neurocognitive function, as well as the cost effectiveness, will be evaluated.

9. STUDY DESIGN

This is a phase II, registry-based, multicentre, parallel group randomised controlled trial, which will allocate patients on V-A ECMO in a 1:1 ratio to either a conservative or liberal oxygen strategy.

10. STUDY POPULATION

10.1 Study Sites

Up to sixteen ECMO centres in Australia and New Zealand. Australian sites include: The Alfred Hospital, The Prince Charles Hospital, Royal Prince Alfred Hospital, St Vincent's Hospital (Sydney), Royal Melbourne Hospital, Fiona Stanley Hospital, The Austin Hospital, Geelong University Hospital, Monash Medical Centre, The Royal Adelaide Hospital, Flinders Medical Centre, Gold Coast hospital, Princess Alexandra Hospital, The Royal North Shore Hospital, Box Hill Hospital and New Zealand sites - Auckland City Hospital.

10.2 Inclusion Criteria

Patients ≥ 18 years who are commenced on V-A ECMO for severe cardiac or following refractory cardiac arrest.

10.3 Exclusion Criteria

- a) Greater than 6 hours have elapsed from the time of initiation of ECMO to randomisation
- b) Patients who are suspected or confirmed to be pregnant
- c) Where an indication exists for a specific oxygen target as part of clinical care (e.g. carbon monoxide poisoning)
- d) Patients who are already enrolled in another oxygen titration study
- e) Patients not willing to receive blood products (e.g. Jehovah's Witness)
- f) Where the treating physician deems the study is not in the patient's best interest

11. RANDOMISATION, BLINDING AND STUDY INTERVENTION

11.1 Care and Screening Prior to Randomisation

Pre-hospital and pre-ECMO care will not be controlled by the trial. After initiation of V-A ECMO, clinicians or research coordinators will assess the patients for eligibility. Eligible patients will be randomised and allocated to either conservative or liberal oxygen management strategy arm. While the first exclusion criteria states, no greater than 6 hours between initiation of ECMO and randomisation, this is to allow the inclusion of patients that require transportation, enrolment and randomisation should be performed **as soon as possible**.

11.2 Sequence Generation

A permuted block randomisation method will be used with variable block sizes, stratified by site and by the indication (V-A ECMO for cardiac failure or V-A ECMO post-refractory cardiac arrest).

11.3 Allocation Concealment

Central randomisation will be performed using a secure, web-based, randomisation interface accessible 24 hours a day. Randomisation will not be performed until participants fulfil all eligibility criteria and are ready to be assigned to study treatment.

11.4 Randomisation

The allocation sequence will be available via a web-based Redcap software. Participants will be enrolled in the study by ICU doctors, nurses, and research staff, as soon as possible after the initiation of V-A ECMO, and the assigned intervention will be commenced immediately. Following successful randomisation, each patient will be assigned a unique 'patient study number' and their study allocation will be identified. In the event that a patient is admitted from the operating theatre (OT) following the

application of V-A ECMO, the start of the 6 hour window is deemed to be the time the patient left the OT.

11.5 Blinding

It is not feasible to blind treatment providers in the ICU, as is common to all process of care studies conducted in this setting. However, clinicians who care for the patients following discharge from the ICU will not be explicitly informed about allocation. Staff conducting long-term outcome measurements will be blinded to allocation status. All analysis will be undertaken by blinded data managers and statisticians.

11.6 Study Strategies

Each eligible and enrolled participant will be randomised to either a conservative or liberal oxygen strategy while receiving V-A ECMO from randomisation up to day 60.

Target saturations & clinician discretion

The target patient oxygen saturations (SpO_2) in the conservative arm are 92% to 96%. Target patient oxygen saturations (SpO_2) in the liberal arm of the trial are 97-100%. Clinicians may elect to reduce the lower end of the target range if considered clinically appropriate for a patient. Titration of FiO_2 and FbO_2 will otherwise occur as per the protocol with the lower target modified to reflect clinician direction. This may occur in either arm of the trial.

Conservative oxygen strategy

Patients allocated to the conservative oxygen strategy will initially have the ECMO blender oxygen fraction (FbO_2) titrated to target post-oxygenator saturations of 92-96% (FbO_2 is not reduced lower than 0.5). Post-oxygenator ABG's will be taken to assess post-oxygenator saturations. Once the FbO_2 is stable, the ventilator FiO_2 will then be titrated to patient oxygen saturations (SpO_2) of 92-96%.

Liberal oxygen strategy

Patients allocated to the liberal oxygen strategy will have the FbO_2 set at 1.0 at all times. Their ventilator FiO_2 will be titrated to patient oxygen saturations (SpO_2) of 97-100%. If patient oxygen saturations (SpO_2) remain between 97-100% clinicians are advised to reduce FiO_2 on the ventilator to a minimum of 0.5 (FiO_2 is not reduced lower than 0.5).

Management of patient hypoxia

Emergency response procedures, in both allocation groups, are to be conducted as per unit policy and should include but not limited to, a check of ECMO blood and gas flow, a check and possible increase in blender FbO_2 to 1.0, and an increase in ventilator FiO_2 to 1.0.

For both allocation groups if patient oxygen saturations (SpO_2) fall below target range (<92% for conservative strategy and <97% for liberal strategy) the ventilator FiO_2 should be increased first.

In the event that FbO_2 is 1.0 and post-oxygenator saturations remain <92% seek expert advice and consider circuit change.

The site PIs will take primary responsibility for training local staff and will use study tools provided by the co-ordinating centre. Poster education campaigns will be used. Early on-site data monitoring will be performed by an experienced project manager from the co-ordinating centre to ensure protocol compliance is achieved.

11.7 Concomitant Care and Interventions

All other aspects of intensive care management will be according to individual unit practice with no restrictions placed on concomitant care. Similarly, if an increase in inspired oxygen is required for procedures performed in the ICU including (but not limited to) bronchoscopy, suctioning, tracheostomy, transportation or preparation for extubation, this is permitted in both groups.

11.8 Discontinuing ECMO and Ventilator Supports

Patients will continue their allocated protocol while receiving V-A ECMO. In the event the patient is separated from V-A ECMO, they will no longer follow their allocated oxygen management strategy. Management of FiO₂ on the ventilator will then be at the discretion of the treating ICU team.

Patients who are extubated and no longer require mechanical ventilation, but who remain on V-A ECMO will continue their allocated protocol for management of FbO₂ on the oxygenator.

If after discontinuing ECMO, V-A ECMO therapy is re-instituted at any time within the 60 day period from randomisation (even if discharged from ICU or hospital during this period), protocolised care will be re-implemented as per previous oxygen strategy to which they were originally randomised.

If V-A ECMO is re-instituted after the 60-day period, management of FiO₂ on the ventilator and FbO₂ on the oxygenator will be at the discretion of the treating ICU team.

11.9 Safety

All patients in the BLENDER trial will have continuous real-time oxygen saturation monitoring (pulse oximetry) at all times. This will be measured on the patient's right hand, however, if it is difficult to obtain peripheral saturations from the right hand, the following sites should be tried in order: the right ear, nose, left ear, left hand.

Arterial blood gases are routinely performed in patients requiring ECMO. Arterial blood gases should be taken from the right arm. If a left arm arterial line is in place, this should be changed to one in the right arm when possible. If it is not possible to insert a right arm arterial line, peripheral saturations should be recorded from the right arm with blood gas values taken from wherever else possible.

The above schema for measurement of oxygen saturations and arterial blood gases is already standard practice for all patients receiving V-A ECMO.

If a change to the blender oxygen FbO₂ is required a post-oxygenator ABG will be taken to ensure the post-oxygenator saturations remain within the target zone (92-96%). This is also routine practice when adjusting blender oxygen FbO₂. Any required adjustments are made by the bedside staff in accordance with the protocol.

12. STUDY OUTCOMES

12.1 Primary outcome

The primary outcome will be the number of alive and ICU-free days at day 60. ICU free days are defined as the total number of days (or part days) being free of ICU between randomisation and day 60, with the exception that all patients who die by day 60 will be defined as having zero ICU free days.

Time spent in ICU where the patient is 'exit-blocked' (e.g. medically suitable for ward discharge, but awaiting transfer) will be included in total ICU-free days.

12.2 Secondary outcomes

1. Number of alive and ICU-free days at day 60 (accounting for exit block)
2. Hospital mortality
3. ICU mortality
4. Hospital length of stay
5. ICU length of stay
6. Duration of mechanical ventilation
7. Six and twelve month mortality
8. Disability at six and twelve months measured with the World Health Organisation's Disability Assessment Schedule 2.0 12L (Appendix 1.1)

9. Quality of life measured at six and twelve months with the EQ5D-5L (Appendix 1.2)
10. Neurocognitive function assessed at six months with the Montreal Cognitive Outcomes Assessment (MoCA-BLIND) and the Glasgow Coma Scale (Appendix 1.3, Appendix 1.4)
11. Functional ability at six and twelve months with Instrumental Activities of Daily Living (IADL) (Appendix 1.5)

12.3 Tertiary outcomes

1. ECMO circuit life
2. Cost effectiveness

13. STUDY ASSESSMENTS

13.1 Data from Clinical Registries

The following data will be collected from existing clinical registries (ANZICS-APD, EXCEL):

1. Demographics (age, sex, functional comorbidities)
2. ICU admission diagnosis
3. Admission category (elective or emergency surgical, medical)
4. APACHE-II/III, RESO and SAVE (illness severity) scores
5. ECMO configuration and settings
6. Outcome measures (ICU, hospital and six- and twelve-month mortality, ICU and Hospital length of stay, six- and twelve-month functional outcomes)

The EXCEL registry is a comprehensive national registry on the treatment and outcomes of patients requiring ECMO, and is coordinated by the ANZIC-RC, Monash University.

13.2 Data quality and standardisation

Data quality and protocol standardisation will be optimised by arranging a start-up meeting and by providing an early monitoring visit (after first 2-4 patients have been enrolled in the trial) and regular feedback to each centre via phone, the trial web-site, and a regular newsletter update.

All study personnel will have access to the study coordinating centre to resolve any questions that might arise. Data transfer and storage will follow the requirements of the approving Human Research Ethics Committee (HREC) and site research governance officers.

14. STATISTICAL METHODS

All analyses will be conducted on an intention-to-treat basis. Data will be assessed for normality, with group comparison performed using Chi-square tests for equal proportion (or Fisher's Exact tests where numbers are small), student t-tests for normally distributed data and Wilcoxon rank sum tests otherwise. The primary outcome, ICU-free days to day 60 will be summarised using medians and interquartile ranges in each treatment arm. Comparison of ICU-free days across treatment arms will be performed using quantile regression, with the principal analysis being median regression (to estimate the difference in median number of days, with P-value and 95% CI) and supplementary analyses using the 25th and 75th percentiles. Binomial outcomes will be analysed using logistic regression and reported as odds ratios (95% CI) while duration variables (Ventilation, ECMO, ICU and hospital stay) will be log-transformed and analysed using linear mixed modelling with results reported as geometric means and ratios (95% CI). While the principal analysis will be performed without adjustment, additional hierarchical multivariable analysis will be conducted to account for potential heterogeneity between stratifying variables (sites and ECMO type), baseline imbalances between treatment arms and a priori defined variables known to influence outcome. All analysis will be performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and a two sided p-value of 0.05 will be used to indicate statistical significance. In accordance with good research practice, a detailed statistical analysis plan will be published prior to study completion.

Power Calculations and Sample Size: Our sample size calculation is derived from our pilot data, where the overall mean ICU-free days to day 60 (in survivors) was 11 days (standard oxygen strategy). Using a type I error rate of 0.05 and a 3 day difference between the groups in ICU-free days (a conservative estimate being less than half the point estimate found in our pilot data), recruiting 124 patients per group will achieve 80% power to detect the specified difference. To account for the fact that ICU-free days are unlikely to be normally distributed, the sample size will be inflated by 15% to 286 patients in accordance with Lehmann.¹⁴ A further 14 patients were added to allow for 5% loss to follow up. Our total intended sample size is 300 patients. The proposed minimum difference of 3 ICU-free days is a realistic, clinically and economically meaningful treatment effect.

15. CO-ENROLMENT

Study participants may be included in any observational trial, which does not affect protocol adherence in the BLENDER trial. Pursuant to approval by the BLENDER Steering Committee, co-enrolment in other randomised or interventional trials may be possible. Approval will be granted by the steering committee on a case-by-case basis.

Co-enrolment with the EXACT trial (NCT03138005), a phase III multicentre, randomised, controlled investigating if reducing oxygen administration to target a normal level as soon as possible following successful resuscitation from out-of-hospital cardiac arrest, compared to current practice of maintain 100% oxygen, will NOT be possible.

16. SITE MANAGEMENT AND GOVERNANCE

The investigator team, including all CIs and AIs, will form the management committee that is responsible for the conduct and coordination of the trial. A steering committee, which includes several members of the management committee, will also be formed. This will enable frequent meetings for providing monitoring and guidance. The investigator team has extensive experience in conducting clinical trials, as does the ANZIC-RC, a world-leading centre in critical care RCTs, which will host the study. Each study centre will have a Principal Investigator and a Research Co-ordinator assigned to the study. All site investigators will be supported by extensive educational material and seven days per week availability of trial staff, if required.

17. DATA MONITORING

17.1 Composition and governance

An independent Data Safety Monitoring Committee (DSMC), consisting of experts in intensive care, clinical research and biostatistics will be established before patient enrolment and will review all trial protocols. A set of DSMC guidelines and a DSMC Charter will be prepared by the study management committee and signed by the members of the DSMC before the trial commences.

17.2 Interim Analysis

A protocol analysis is planned after recruitment of 50 participants. The purpose of this is to ensure clinically important separation of oxygen exposure between treatment groups, with minimal protocol violations. Outcome data will not be reviewed at this point. A further interim safety analysis will be performed once 60-day outcome data for 150 participants are available. The sample size has been adequately inflated to allow for this single interim analysis.

18. SAFETY AND REPORTING

It is recognised that patients on V-A ECMO will experience a number of aberrations in laboratory values, signs and symptoms due to the severity of the underlying disease and the impact of ECMO support. These will not necessarily constitute an adverse event or serious adverse event unless they are considered to be related to study treatment or a concern in the principal investigator's clinical judgement. In this study, report of adverse events will be restricted to events that are considered to be related to the study intervention (possibly, probably or definitely).

18.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical trial subject. Untoward medical occurrences are common in patients who are supported on V-A ECMO and treated in intensive care. This critically ill group of patients will be monitored and treated for untoward medical occurrences, and this is considered standard care. Therefore, only adverse events which the treating clinician believes are

associated with the intervention will be reported.

18.2 Serious adverse events

A serious adverse event (SAE) is defined as any adverse event that:

- Results in death
- Is life threatening
- Requires hospitalisation or prolongation of current hospitalisation
- Results in persistent or significant disability or incapacity

Death is an expected outcome in patients on V-A ECMO. Approximately 30-60% of patients will not survive to 6 months, therefore a death itself will not necessarily be considered a serious adverse event (SAE) unless considered a potential consequence of being in the BLENDER trial. Caring for V-A ECMO patients includes a host of complications that fit the definition of an SAE. Complications potentially attributable to the BLENDER intervention include hypoxia episodes. Therefore, the following will be considered serious adverse events:

18.3 Specific serious adverse events

- Seizure
- CPR required
- Any critical hypoxic episode ($\text{SpO}_2 < 80\%$) requiring an emergency response

18.4 Reporting SAEs

All SAE's from randomisation to cessation of V-A ECMO will be recorded on Redcap and on a paper SAE reporting form and reported to coordinating centre within 24 hours.

The minimum information to report will include:

- Patient initials and study number
- Nature of the event
- Commencement and cessation of the event
- The principal or co-investigator's opinion of the relationship between the study intervention and the event (not related, possibly related or probably related)
- Whether treatment was required for the event and what treatment was administered.

It is the responsibility of each principal investigator to inform the chief investigator, project manager at coordinating centre, and local HREC of all SAEs which occur at their hospital, in accordance with local requirements. Copies of any reporting and correspondence to and from the local HREC or RGO should also be sent to the coordinating centre. The coordinating centre staff will be responsible for, reporting SAE's to the lead HREC and alerting other participating sites of the SAE if deemed required.

19. CONSENT AND ETHICAL CONSIDERATIONS

19.1 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.

19.2 Human research ethics committee review

The protocol for this project will be reviewed by a lead human research ethics committee (HREC). Each principal investigator will then be responsible for applying for local research governance approval at each participating site. Documentation of the approval of the protocol and the consent documents will be

provided to the coordinating centre before the study may begin at any investigative centre.

The coordinating centre will assist with this process by preparing a standard application form (in Australia, the National Ethics Application Form [NEAF] or HREA [equivalent]; in New Zealand, the National Application Form) and template consent documents. The content and format of the standard information statements information brochure will be adapted if necessary to comply with local HREC guidelines and requirements. During the trial, any amendment or modification to the study protocol or consent documents will be notified to the HREC by the principal investigator and only implemented on receipt of HREC approval, unless the change is necessary to eliminate an immediate hazard to patients, in which case the HREC will be informed as soon as possible. The principal investigator will also be responsible for submitting progress reports, adverse event reports, and any other required documentation to the HREC in accordance with their guidelines. Copies of all HREC and research governance officer correspondence will be provided to the coordinating centre together with a copy of the approved consent documents. Copies of the same documents will also be kept with the study investigator files.

19.3 Consent procedures

The NHMRC National Statement on the Ethical Conduct of Research in Humans (March 2007)¹⁵ acknowledges in Chapter 4.4 that research involving patients who are heavily dependent on medical care, such as the patients in this study, is necessary to assess and improve the efficacy and safety of interventions used in their treatment. This project involves emergency care research; recruitment has to be achieved rapidly as V-A ECMO is a lifesaving, time critical treatment, to which oxygen application is an essential element. By virtue of the inclusion criteria, and that all patients should be enrolled and randomised as a matter of urgency after initiation of ECMO, it is not feasible to obtain informed consent prior to enrolment. The reasons for this are due to:

1. The severity of the patient's condition- often in extremis are unconscious or sedated.
2. The patient should be randomised **as soon as possible** following initiation of V-A ECMO.
3. The emergency situation surrounding the patient requiring V-A ECMO (e.g. out of hospital cardiac arrest) often the person responsible/MTDM is unavailable.
4. This is a traumatic time for family members, and seeking prospective consent creates an additional burden for these distressed family members.
5. The concerns over the validity of a consent obtained under these highly stressful and emotional conditions.

The potential benefits to society are significant, it is impractical to obtain consent given the emergency nature of the treatment, the study involves no investigational drug, both arms of treatment are within current practice, and there is no known reason for thinking the participants would not have consented if asked.

As soon as practicable following recruitment the participant and/or their legally authorised representative will be informed of the participant's inclusion in the research. The site investigators/research coordinators will provide the participant and/or their legally authorised representative with an information brochure which will detail, the nature of the research project, their participation, and the procedure to withdraw from the research project including contact details for those who wish to request additional information.

Any interaction between research staff, participants and their person responsible will take into consideration the stress or emotional factors associated with critical illness and ensure that the dependency of potential participants and their relatives on medical personnel providing treatment does not compromise the freedom of the decision to continue participation (4.4.11).

19.3.1 Consent procedure in the state of Victoria

Enrolment in this project, which involves an emergency medical research procedure, will be performed under Section 53 of the Victorian Medical Treatment Planning and Decisions (MTPD) Act 2016. Consent

will not be sought from the patients or their medical decision maker prior to patients' enrolment in the study. A waiver of consent has been granted by the HREC for the collection of data required by the BLENDER trial, which is in addition to the data collected by the registries. When appropriate the participant/MTDM is informed of their involvement in and of their right to withdraw from the BLENDER trial (see SOP for consent process in Victoria).

19.3.2 Consent procedure in the state of Queensland

The Trial is not a comparative assessment of health care already proven to be beneficial (as set out in section 13(1A) of Schedule 2 of the GA Act QLD), the Trial falls within the definition of "clinical research" as set out in section 13(1) of Schedule 2 of the *Guardianship and Administration Act 2000* (Qld) (**GA Act QLD**). Therefore, the Trial will require approval by the Queensland Civil and Administrative Tribunal (**QCAT**).

Provided that the Trial meets the particular conditions for approval of clinical research by QCAT (as set out in section 13(3) of Schedule 2 of the GA Act QLD which includes obtaining Human Research Ethics Committee approval), enrolment of participants in Queensland can proceed under approved clinical research constituting "urgent health care" in accordance with the GA Act QLD.

19.3.3 Consent procedure in the state of South Australia

The Trial falls within the definition of "medical treatment" as set out in section 4(1) of the *Consent to Medical Treatment and Palliative Care Act 1995* (SA) (**CMTPC Act**). The enrolment of South Australian participants in the Trial can therefore proceed under medical treatment constituting "emergency medical treatment" in accordance with the CMTPC Act

19.3.4 Consent procedure in the state of New South Wales

The Trial does not fall within the definition of a "clinical trial" under section 33(1) of the *Guardianship Act 1987* (NSW) (**GA Act**) because it does not involve an assessment of new medical treatment, or procedures that seek to assess a non-standard treatment or a non-standard application of an accepted treatment. The enrolment of participants in New South Wales can therefore proceed under medical treatment necessary as a "matter of urgency" to save the patient's life or to prevent serious damage to the patient's health in accordance with section 37(1) of the GA Act.

19.3.5 Consent procedure in the state of Western Australia

The Trial falls within the definition of "treatment", in particular "medical or surgical treatment" as set out in section 3(1) of the *Guardianship and Administration Act 1990* (WA) (**GA Act WA**). The enrolment of participants in Western Australia can therefore proceed on the basis that the Trial constitutes "urgent treatment" in accordance with section 110ZH of the GA Act WA.

19.4 Confidentiality and privacy

All participant data pertaining to the study will be stored in a secure, password protected, computer database at Monash University and will maintain confidentiality in accordance with local legislation on privacy and use of health data. The BLENDER trial has been granted a waiver of consent for data collection. This waiver covers the data required for randomisation, safety and compliance monitoring and is in addition to the data collected by the registries. This data will be collected at the site and stored by the research coordinators in a secure locked location. De-identified data will be transferred to the secure database at Monash University as it is entered by the sites. In the event that the data has been transferred prior to the withdrawal of a participant we intend to delete this data. Participant data can be withdrawn at any point prior to the analysis of the research data. The data of a participant who withdraws will be destroyed and a note will be written in the patient site history to this effect. This data will not be used for any analysis of BLENDER, except to report the number of withdrawals from the study. When archiving or processing any data pertaining to the investigator and/or to the participants, the coordinating centre will take all appropriate measures to safeguard and prevent access to this data by

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any un-authorised third party.

The investigator will maintain the confidentiality of all study documentation, and take measures to prevent accidental or premature destruction of these documents. The investigator will retain the study documents for at least 15 years after the completion or discontinuation of the study. The investigator must notify the study management committee prior to destroying any study essential documents following the study completion or discontinuation. If the investigator's personal situation is such that archiving can no longer be ensured by him/her, the investigator shall inform the study management committee and the relevant records shall be transferred to a mutually agreed upon designee. If any investigator retires, relocates, or otherwise withdraws from conducting a study, the responsibility for maintaining records may be transferred to the coordinating centre, or another investigator.

20. QUALITY ASSURANCE

The study will be conducted in accordance with the ICH Guidelines for Good Clinical Practice (GCP) and with all relevant local and national regulations.

20.1 Investigator file

A file containing essential documents as outlined in the ICH Guidelines for GCP will be maintained at each participating site. A copy of the same documents will be held at the coordinating centre.

20.2 Study materials

A comprehensive guide to the data collection with definitions and rationale will be provided together with a paper version of the data collection forms. This education will be provided in conjunction with education for the EXCEL registry data collection as the BLENDER trial intends on extrapolating the majority of their data points from this registry.

20.3 Initiation

All site personnel will receive training, explaining the protocol and procedures, use of the web-based randomisation system, and reporting protocol deviations and SAEs. The Site 'initiation visit' will be conducted by teleconference or video conference or face-to-face meeting at the participating site. Written and electronic materials will be supplied for study staff and for the education of clinical ICU staff at each participating site.

20.4 Monitoring during the study

A coordinating centre monitor will visit each study centre early in the recruitment phase (after first 2-4 patient have been enrolled). This will ensure that the study is conducted according to the protocol, good clinical practice guidelines and relevant regional regulatory requirements. The study monitor will review study records for source document verification, confirm valid patient consents, and data quality. In addition, the study may also be audited by local or national regulatory authorities. Access to source documents and other study files will be made available at all study centres for monitoring and audit purposes.

The coordinating centre team will conduct regular remote monitoring on the web-based database by applying validation and consistency rules and with regular data cleaning to ensure the integrity of the study data.

20.5 Close out

At completion of the study, the monitor will ensure that there are plans in place for the long-term storage of all the relevant data and source documentation (for 15 years).

21. INVESTIGATOR RESPONSIBILITIES

The trial site investigator is responsible for:

- Screening and listing eligible patients
- Performing randomisation
- Achieving conservative and liberal oxygenation strategies according to allocation group
- Ensuring the intervention is delivered as soon as possible.
- Maintaining oxygenation strategies according to allocation group
- Collection and reporting of data according to the trial protocol and electronic case report form (eCRF)
- Obtaining written informed consent from patients whom regain consciousness
- Performing and reporting follow-up according to the trial protocol and the eCRF

The steering committee is responsible for:

- Coordination of national sites
- Reviewing reasons for potential incomplete screening and randomisation at national sites
- Ethical Review Board – application and approval
- Dissemination of protocols and updates to sites
- Proposing suitable candidates for vacant site investigator positions

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APPENDICIES

APPENDIX 1.1

6 MONTH FOLLOW-UP ASSESSMENT



WHODAS 2.0

WORLD HEALTH ORGANIZATION
DISABILITY ASSESSMENT SCHEDULE 2.0

12

Interview

Section 2 Demographic and background information

This interview has been developed by the World Health Organization (WHO) to better understand the difficulties people may have due to their health conditions. The information that you provide in this interview is confidential and will be used only for research. The interview will take 5–10 minutes to complete.

For respondents from the general population (not the clinical population) say:

Even if you are healthy and have no difficulties, I need to ask all of the questions so that the survey is complete.

I will start with some background questions.

A1	Record sex as observed	Female	1
		Male	2
A2	How old are you now?	_____ years	
A3	How many years in all did you spend <u>studying in school, college or university</u> ?	_____ years	
A4	What is your <u>current marital status</u>? (Select the single best option)	Never married	1
		Currently married	2
		Separated	3
		Divorced	4
		Widowed	5
		Cohabiting	6
A5	Which describes your <u>main work status</u> best? (Select the single best option)	Paid work	1
		Self-employed, such as own your business or farming	2
		Non-paid work, such as volunteer or charity	3
		Student	4
		Keeping house/ homemaker	5
		Retired	6
		Unemployed (health reasons)	7
		Unemployed (other reasons)	8
		Other (specify) _____	9

Please continue to next page...

**Section 4 Core questions***Show flashcard #2*

In the past 30 days, how much difficulty did you have in:		None	Mild	Moderate	Severe	Extreme or cannot do
S1	<u>Standing for long periods</u> such as <u>30 minutes</u> ?	1	2	3	4	5
S2	Taking care of your <u>household responsibilities</u> ?	1	2	3	4	5
S3	<u>Learning a new task</u> , for example, learning how to get to a new place?	1	2	3	4	5
S4	How much of a problem did you have <u>joining in community activities</u> (for example, festivities, religious or other activities) in the same way as anyone else can?	1	2	3	4	5
S5	How much have you been <u>emotionally affected</u> by your health problems?	1	2	3	4	5

In the past 30 days, how much difficulty did you have in:		None	Mild	Moderate	Severe	Extreme or cannot do
S6	<u>Concentrating on doing something for ten minutes</u> ?	1	2	3	4	5
S7	<u>Walking a long distance</u> such as a <u>kilometre</u> [or equivalent]?	1	2	3	4	5
S8	<u>Washing your whole body</u> ?	1	2	3	4	5
S9	Getting <u>dressed</u> ?	1	2	3	4	5
S10	<u>Dealing with people you do not know</u> ?	1	2	3	4	5
S11	<u>Maintaining a friendship</u> ?	1	2	3	4	5
S12	Your day-to-day <u>work/school</u> ?	1	2	3	4	5

H1	Overall, in the past 30 days, <u>how many days</u> were these difficulties present?	<i>Record number of days</i> ____
H2	In the past 30 days, for how many days were you <u>totally unable</u> to carry out your usual activities or work because of any health condition?	<i>Record number of days</i> ____
H3	In the past 30 days, not counting the days that you were totally unable, for how many days did you <u>cut back</u> or <u>reduce</u> your usual activities or work because of any health condition?	<i>Record number of days</i> ____

This concludes our interview. Thank you for participating.

APPENDIX 1.2 Euro QoL Group Health Survey (EQ-5D-5L)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems with walking around ☐
- I have slight problems with walking around ☐
- I have moderate problems with walking around ☐
- I have severe problems with walking around ☐
- I am unable to walk around ☐

PERSONAL CARE

- I have no problems with washing or dressing myself ☐
- I have slight problems with washing or dressing myself ☐
- I have moderate problems with washing or dressing myself ☐
- I have severe problems with washing or dressing myself ☐
- I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

PAIN / DISCOMFORT

- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

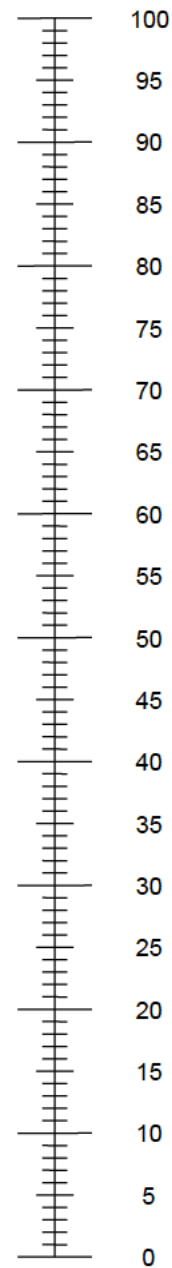
ANXIETY / DEPRESSION

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health
you can imagine



The worst health
you can imagine

APPENDIX 1.3: Montreal Cognitive Assessment

MONTREAL COGNITIVE ASSESSMENT / MoCA-BLIND

Version 7.1 Original Version

Name:

Education:

Sex:

Date of birth:

Date:

MEMORY			FACE	VELVET	CHURCH	DAISY	RED	POINTS
Read list of words, subject must repeat them. Do 2 trials even if 1st trial is successful. Do a recall after 5 minutes.		1st trial						No points
		2nd trial						
ATTENTION								
Read list of digits (1 digit/sec.) Subject has to repeat them in the forward order		[] 2 1 8 5 4						___/ 2
Subject has to repeat them in the backward order		[] 7 4 2						
Read list of letters. The subject must tap with his hand at each letter A. No point if ≥ 2 errors		[] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B						___/ 1
Serial 7 subtraction starting at 100		[] 93 [] 86 [] 79 [] 72 [] 65						___/ 3
4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt								
LANGUAGE								
Repeat: I only know that John is the one to help today. []								___/ 2
The cat always hid under the couch when dogs were in the room. []								
Fluency / Name maximum number of words in one minute that begin with the letter F.		[] _____ (N $\geq$ 11 words)						___/ 1
ABSTRACTION		[] train - bicycle						___/ 2
Similarity between e.g. banana - orange = fruit		[] watch - ruler						
DELAYED RECALL	Has to recall words	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUEDE recall only	___/ 5
	With no cue	[]	[]	[]	[]	[]		
Optional	Category cue							
	Multiple choice cue							
ORIENTATION		[] Date [] Month [] Year [] Day [] Place [] City						___/ 6
© Z. Nasreddine MD		www.mocatest.org		Normal $\geq$ 18 / 22		TOTAL		___/ 22
Administered by: _____						Add 1 point if $\leq$ 12 yr edu		

APPENDIX 1.4 Glasgow Coma Scale Extended (GOSE)

The Glasgow Outcome Scale (GOS) is a global scale for functional outcome that rates patient status into one of five categories: Dead, Vegetative State, Severe Disability, Moderate Disability, or Good Recovery. The extended GOS (GOSE) provides more detailed categorisation into eight categories by subdividing the categories of severe disability, moderate disability, and good recovery into a lower and upper category:

1	Death	D
2	Vegetative state	VS
3	Lower severe disability	SD-
4	Upper severe disability	SD+
5	Lower moderate disability	MD-
6	Upper moderate disability	MD+
7	Lower good recovery	GR-
8	Upper good recovery	GR+

For each question please select the response that best describes your answer by marking the appropriate box.

Respondent (please tick):

- ☐ Patient alone
- ☐ Relative/friend/carer alone
- ☐ Patient + relative/friend/carer

CONSCIOUSNESS

1. Is the head injured person able to obey simple commands, or say any words?

- ☐ Yes
- ☐ No (VS)

INDEPENDENCE IN THE HOME

2a. Is the assistance of another person at home essential every day for some activities of daily living?

- ☐ Yes
- ☐ No If no: go to 2c

Note: for a 'No' answer they should be able to look after themselves at home for 24 hours if necessary, though they need not actually look after themselves. Independence includes the ability to plan for and carry out the following activities: getting washed, putting on clean clothes without prompting, preparing food for themselves, dealing with

callers, and handling minor domestic crises. The person should be able to carry out activities without needing prompting or reminding and should be capable of being left alone overnight.

2b. Do you need frequent help or someone to be around at home most of the time?

- ☐ Yes (lower SD)
- ☐ No (upper SD)

Note: for a 'No' answer they should be able to look after themselves at home for up to 8 hours during the day if necessary, though they need not actually look after themselves.

2c. Was assistance at home essential before the injury?

- ☐ Yes
- ☐ No

INDEPENDENCE OUTSIDE THE HOME

3a. Are you able to shop without assistance?

- ☐ Yes
- ☐ No (upper SD)

Note: this includes being able to plan what to buy, take care of money themselves and behave appropriately in public. They need not normally shop, but must be able to do so.

3b. Were you able to shop without assistance before the injury?

- ☐ Yes
- ☐ No

4a. Are you able to travel locally without assistance?

- ☐ Yes
- ☐ No (upper SD)

Note: they may drive or use public transport to get around. Ability to use taxi is sufficient, provided the person can phone for it themselves and instruct the driver.

4b. Were you able to travel without assistance before the injury?

- ☐ Yes
- ☐ No

WORK

5a. Are you currently able to work to your previous capacity?

- ☐ Yes If yes, go to 5c
- ☐ No

Note: if they were working before, then their current capacity for work should be at the same level. If they were seeking work before, then the injury should not have adversely affected their chances of obtaining work or the level of work for which they are eligible. If the patient was a student before injury then their capacity for study should not have been adversely affected.

5b. How restricted are you?

- ☐ Reduced work capacity (upper MD)
- ☐ Able to work only in sheltered workshop or non-competitive job or currently unable to work (lower MD)

5c. Were you either working or seeking employment before the injury?

- ☐ Yes
- ☐ No

SOCIAL AND LEISURE ACTIVITIES

6a. Are you able to resume regular social and leisure activities outside home?

- ☐ Yes If yes, go to 6c
☐ No

Note: they need not have resumed all their previous leisure activities, but should not be prevented by physical or mental impairment. If they have stopped the majority of activities because of loss of interest or motivation than this is also considered as a 'No' answer.

6b. What is the extent of restriction on your social and leisure activities?

- ☐ Participate a bit less: at least half as often as before injury. (Lower GR)
☐ Participate much less: less than half as often. (Upper MD)
☐ Unable to participate: rarely, if ever, take part. (Lower MD)

6c. Did you engage in regular social and leisure activities outside home before injury?

- ☐ Yes
☐ No

FAMILY AND FRIENDS

7a. Have there been psychological problems which have resulted in ongoing family disruption or disruption to friendships?

- ☐ Yes If yes, go to 7c
☐ No

Note: typical post-traumatic personality changes: quick temper, irritability, anxiety, insensitivity to others, mood swings, depression and unreasonable or childish behaviour.

7b. What has been the extent of disruption or strain?

- ☐ Occasional – less than weekly (Lower GR)
☐ Frequent – once a week or more, but not tolerable (Upper MD)
☐ Constant – daily and intolerable (Lower MD)

7c. Were there problems with family or friends before the injury?

- ☐ Yes
☐ No

Note: if there were some problems before injury, but these have become markedly worse since injury please answer 'No'.

RETURN TO NORMAL LIFE

8a. Are there any other current problems relating to the injury which affect daily life?

- ☐ Yes (Lower GR)
☐ No (Upper GR) If no, go to 9

Note: other typical problems reported after head injury: headaches, dizziness, tiredness, sensitivity to noise or light, slowness, memory failures and concentration problems.

8b. Were similar problems present before the injury?

- ☐ Yes
☐ No

Note: if there were some problems before injury, but these have become markedly worse since injury then please answer 'No'.

APPENDIX 1.5: Instrumental Activities of Daily Living (IADL)

Instrumental Activities of Daily Living (IADL)

Instructions: Circle the scoring point for the statement that most closely corresponds to the patient's current functional ability for each task. The examiner should complete the scale based on information about the patient from the patient him-/herself, informants (such as the patient's family member or other caregiver), and recent records.

A. Ability to use telephone	Score	E. Laundry	Score
1. Operates telephone on own initiative; looks up and dials numbers, etc.	1	1. Does personal laundry completely	1
2. Dials a few well-known numbers	1	2. Launders small items; rinses stockings, etc.	1
3. Answers telephone but does not dial	1	3. All laundry must be done by others	0
4. Does not use telephone at all	0		
B. Shopping		F. Mode of transportation	
1. Takes care of all shopping needs independently	1	1. Travels independently on public transportation or drives own car	1
2. Shops independently for small purchases	0	2. Arranges own travel via taxi, but does not otherwise use public transportation	1
3. Needs to be accompanied on any shopping trip	0	3. Travels on public transportation when assisted or accompanied by another	1
4. Completely unable to shop	0	4. Travel limited to taxi or automobile with assistance of another	0
		5. Does not travel at all	0
C. Food preparation		G. Responsibility for own medications	
1. Plans, prepares, and serves adequate meals independently	1	1. Is responsible for taking medication in correct dosages at correct time	1
2. Prepares adequate meals if supplied with ingredients	0	2. Takes responsibility if medication is prepared in advance in separate dosages	0
3. Heats and serves prepared meals, or prepares meals but does not maintain adequate diet	0	3. Is not capable of dispensing own medication	0
4. Needs to have meals prepared and served	0	H. Ability to handle finances	
D. Housekeeping		1. Manages financial matters independently (budgets, writes checks, pays rent and bills, goes to bank), collects and keeps track of income	1
1. Maintains house alone or with occasional assistance (e.g., "heavy work domestic help")	1	2. Manages day-to-day purchases, but needs help with banking, major purchases, etc.	1
2. Performs light daily tasks such as dishwashing, bed making	1	3. Incapable of handling money	0
3. Performs light daily tasks but cannot maintain acceptable level of cleanliness	1		
4. Needs help with all home maintenance tasks	1		
5. Does not participate in any housekeeping tasks	0		

(Lawton & Brody, 1969)

Scoring: The patient receives a score of 1 for each item labeled A – H if his or her competence is rated at some minimal level or higher. Add the total points circled for A – H. The total score may range from 0 – 8. A lower score indicates a higher level of dependence.

Sources:

- Cromwell DA, Eagar K, Poulos RG. The performance of instrumental activities of daily living scale in screening for cognitive impairment in elderly community residents. *J Clin Epidemiol.* 2003;56(2):131-137.
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- Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist.* 1969;9(3):179-186.
- Polisher Research Institute. Instrumental Activities of Daily Living Scale (IADL). Available at: <http://www.abramsoncenter.org/PRI/documents/IADL.pdf>. Accessed February 15, 2005.

APPENDIX 2.0: Proposed Research Timeframe

Expected timeframe	Milestone
Year 2019	
Monthly	Management meetings to discuss recruitment and interstate coordination
February	HREC application submitted
June	Site initiation visit at the Alfred
July	Commence RGO applications for other sites
August	Monitor visits commenced at first site
September	Site initiation visits and training at other Victorian sites
October	Patients enrolled across Victorian sites
October	RGO applications for NSW and QLD sites
November	Monitor visits commenced at Victorian sites
December	Six-month follow ups will be commenced and completed by EXCEL registry
November	Report 1 to the Commonwealth representative
Year 2020	
Monthly	Management meetings to discuss recruitment and interstate coordination
January	Site initiation visits at NSW and QLD sites
February	Enrolled patients across NSW and QLD
February	Ongoing Monitor for quality and protocol compliance at each site
February	Ongoing training and recruitment management at sites
March	HREC annual report
November	Monitor visits commenced at NSW and QLD sites
November	Report 2 to the Commonwealth representative
November	Ethics approval for WA sites
December	Site initiation visits in WA sites
December	Enrolment in WA sites
Year 2021	
Monthly	Management meetings to discuss recruitment and interstate coordination
January-December	Ongoing Monitor for quality and protocol compliance at each site
January-December	Ongoing training and recruitment management at sites
March	HREC annual report
June	Interim analysis (N=150 after 6-month analysis completed)
November	Report 3 to the Commonwealth representative
Year 2022	
Monthly	Management meetings to discuss recruitment and interstate coordination
January-December	Ongoing Monitor for quality and protocol compliance at each site
January-December	Ongoing training and recruitment management at sites
March	HREC annual report
November	Report 4 to the Commonwealth representative
Year 2023	
Monthly	Management meetings to discuss site close outs, data cleaning and analysis
January	Ongoing Monitor for quality and protocol compliance at each site
September	Long-term follow ups completed for all enrolled patients
September	Close out of sites and final HREC report completed
September	Data cleaning and analysis
November	Placement of data in a repository
November	Final report to the Commonwealth representative
December	Submitted for publication