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Complete List of Authors:	Rai, Sumeet; Canberra Hospital, Intensive Care Unit; Australian National University, Medical School Brown, Rhonda; Australian National University Research School of Psychology, Van Haren, Frank; Canberra Hospital, Intensive Care; University of Canberra Faculty of Health Neeman, Teresa; Australian National University, Statistical Consulting Unit Rajamani, Arvind; Nepean Hospital, Intensive Care; University of Sydney - Sydney Medical School Nepean Sundararajan, Krishnaswamy; Royal Adelaide Hospital; University of Adelaide, Discipline of Acute Care Medicine Mitchell, Imogen; The Canberra Hospital, Intensive Care; Australian National University, Medical School
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Long-term follow up for Psychological stRess in Intensive CarE survivors (PRICE): study protocol for a multicentre, prospective observational cohort study in Australian intensive care units

Sumeet Rai, Rhonda Brown, Frank van Haren, Teresa Neeman, Arvind Rajamani, Krishnaswamy Sundararajan, Imogen Mitchell

Author details:

Sumeet Rai: Intensivist[1], Clinical lecturer[2] and PhD doctoral candidate[2]

Rhonda Brown: Associate Professor[3]

Frank van Haren: Intensivist[1], Adjunct Professor[4]

Teresa M Neeman: Statistical consultant[5]

Arvind Rajamani: Intensivist[6], Clinical Lecturer[7]

Krishnaswamy Sundararajan: Intensivist[8], Senior Clinical Lecturer[9]

Imogen Mitchell: Intensivist[1], Professor[2] & Dean[2]

1. Canberra Hospital Intensive Care Unit, Garran, Canberra, Australia
2. Australian National University Medical School, Canberra, Australia
3. Research School of Psychology, Australian National University, Canberra, Australia
4. University of Canberra, Bruce, Canberra, Australia
5. Statistical Consulting Unit, Australian National University, Canberra, Australia
6. Nepean Hospital, Kingswood, Sydney, Australia
7. University of Sydney, Sydney, Australia
8. Royal Adelaide Hospital, Adelaide, Australia
9. Discipline of Acute Care Medicine, University of Adelaide, Adelaide, Australia

Address for correspondence:

Sumeet Rai
Intensive Care Unit, Canberra Hospital, Yamba Drive, Garran, ACT, Canberra, Australia 2605
E-mail: Sumeet.Rai@act.gov.au

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Abstract

Introduction There are little published data on the long-term psychological outcomes in intensive care unit (ICU) survivors and their family members in Australian ICUs. In addition, there is scant literature evaluating the effects of psychological consequences of intensive care survivors on their family members. The aims of this study are to describe and compare the long-term psychological outcomes of intubated and non-intubated ICU survivors and their family members.

Methods and analysis This will be a prospective observational cohort study across four ICUs in Australia. The study aims to recruit 150 (75 intubated and 75 non-intubated) adult ICU survivors and 150 family members of the survivors from 2015-2018. Long-term psychological outcomes and effects on health-related quality of life (HRQoL) will be evaluated at 3 and 12 months follow up using validated and published screening tools. The primary objective is to compare the prevalence of affective symptoms in intubated and non-intubated survivors of intensive care and their families and it's effects on HRQoL.

Ethics and dissemination The study has been approved by the relevant human research ethics committees (HREC) of Australian Capital Territory (ACT) Health (ETH.11.14.315), New South Wales (HREC/16/HNE/64), South Australia (HREC/15/RAH/346). The results of this study will be published in a peer-reviewed medical journal and presented to the local intensive care community and other stakeholders.

Trial registration number: Australian New Zealand Clinical Trials Registry (ACTRN12615000880549)

Strengths and limitations of this study:

The study will be a multi-centre, prospective observational cohort trial assessing long-term (12 months) psychological outcomes in ICU survivors and family members, adding valuable data on long-term outcomes for the post-ICU patients and family.

The study includes a diverse ICU patient population (intubated and non-intubated), as non-intubated patient outcomes have previously not been vigorously studied.

The study design includes paired samples of ICU survivors and their family members to explore whether there is a relationship between adverse psychological outcomes in survivors and family members.

The tools adopted to assess psychological and HRQoL outcomes are published and validated.

A significant limitation of the study design is the absence of pre-ICU admission data on affective disorders and health related quality of life among the patients and family members, preventing comparisons with the post-ICU outcomes.

Introduction

Over the last two decades, numerous long-term outcome studies have shown that survivors of critical illness can suffer from a complex myriad of health and socio-economic issues long after discharge from hospital (1-6). Initial seminal studies on long-term outcomes in critical illness are based on survivors of Acute Respiratory Distress Syndrome (ARDS), a condition traditionally treated with invasive ventilation, sedation and muscle relaxants (7-10). Long-term (1 to 5-years) outcomes of acute lung injury and ARDS survivors have been extensively studied (11,12) with emerging evidence of long-term follow-up outcomes in other categories of ICU survivors (3,13,14). The term “post intensive care syndrome” (PICS) was framed to describe new or worsening impairments in physical, cognitive, or mental health status after an episode of critical illness and persisting beyond discharge (15).

Based on the above research, it has been established, beyond reasonable doubt, that a significant proportion of ICU survivors experience long-term psychological consequences, including post-traumatic stress disorder (PTSD), anxiety and depression (16-20). The reported prevalence of adverse neuropsychiatric outcomes in intensive care survivors varies across studies. A recent systematic review of the literature from 2008 - 2012 suggests that up to 27% of ICU survivors suffer from PTSD(21). On the other hand, another recent study from the US found that the prevalence of PTSD in ICU survivors was 16% at 3 months post-ICU (22). A systematic review of the literature reveals that the reported prevalence of anxiety in ICU survivors ranges from 23% to 48% and 17% to 43% for depression (19). Another study shows an incidence of 31% for depressive symptoms post-ICU (22). Literature reviews suggests that severity of illness as evidenced by the length of ICU stay, need for intubation, mechanical ventilation and sedation are high risk factors for psychological stress in ICU survivors (23-26). However, there is very little literature on the incidence of psychological stress post ICU in the patients who do not need sedation, intubation and mechanical ventilation. Interventions to reduce PTSD in ICU survivors have excluded the less severe patient populations (not intubated and ventilated) (27). It is possible the incidence of psychological symptoms in such a population is low but this remains only a conjecture.

Published literature also suggests that a high proportion of family members of intensive care patients are left with varying psychological symptoms that can include anxiety, depression, and PTSD (28-31). Possible precipitating factors include a concern for the patient's chronic illnesses; the current illness necessitating admission to the intensive care unit; the prospect of the death of a loved one, discussion and decisions regarding end-of-life and the prospect of providing continuing care to survivors (32,33). Stress in family members may also be exacerbated by the fact that they remember the ICU experience of their loved one, while the patient may not remember their ICU experience.

To date, there are little data from Australian ICUs about the prevalence of psychological stress in the ICU survivors and their family members. Drawing comparisons on prevalence rates across the continents from studies predominantly originating in America and Europe may not be helpful due to the variation in critical care services (34).

The primary aim of this multicentre study is to determine and compare the prevalence of affective symptoms in intubated and non-intubated ICU survivors and their family members by screening them for PTSD, anxiety, depression and Health Related Quality of Life (HRQoL) over a 12-month follow up period. The secondary aims of this study are to identify the risk factors for adverse psychological outcomes in ICU survivors.

We anticipate that PRICE will provide significant insight into the impact of affective symptoms on post intensive care survivors, especially the non-intubated group and their family members, as they have been previously excluded from studies. This will contribute to the existing body of knowledge and help in identifying risk factors for psychological stress. We hope that this research will allow better understanding of modifiable risk factors and promote further research in improving care for the critically ill intensive care patients and families well after their discharge from intensive care.

Methods and analysis

Study design

PRICE is a multicentre, prospective, observational cohort study reviewing ICU survivors and their family members. The groups will be divided based on the following ICU admission characteristics:
a) Intubated group: Intubated ICU survivor and family member
b) Non-intubated group: Non-intubated ICU survivor and family member.

Setting

The study will be conducted in four Intensive Care Units in Australia: The Canberra Hospital, Australian Capital Territory; Nepean Hospital and John Hunter Hospital, New South Wales and Royal Adelaide Hospital, South Australia. All the four intensive care units are part of large teaching public hospitals. Local principal investigators, in conjunction with a local research team will conduct the trial in their respective hospitals.

Study population

The study population will include adult (18 years and older) ICU survivors and their family members who have been discharged from ICU during the current hospital stay. Detailed inclusion and exclusion criteria are as follows:

Inclusion criteria:
A) Intubated ICU survivor:

- Able to provide consent
- Intubated and mechanically ventilated for more than 24 hours AND
- Stayed in intensive care unit for more than 72 hours

B) Non-intubated ICU survivor:

- Able to provide consent
- Not intubated during current ICU stay
- Received inotropic/vasopressor support and/or non-invasive ventilation during ICU stay

Family Members

- Family member (spouse/partner/next of kin/lives with patient normally) of a consenting ICU patient with above criteria
- Age 18 years and older

Exclusion criteria:

- Prior history of a psychiatric disorder/s in patient (schizoaffective disorders, chronic PTSD)
- Imminent death/palliative care patient (unlikely to be alive at follow up at 3, 12 months)
- Suspected acute primary brain lesion that may result in global impairment of conscious level or cognition, such as traumatic brain injury, intracranial haemorrhage, stroke, or hypoxic brain injury.
- Unable to give informed consent prior to hospital discharge.
- Non-English speaking background.

Patients will be screened for eligibility by the research staff in the participating ICUs after discharge from the ICU. Research staff will approach medical and nursing teams on the hospital wards to seek their permission to approach patients and also to confirm that the patients are not delirious and can provide appropriate consent. They will then meet with the patients and their family members to explain the study and provide them with the study information sheet (supplementary file, appendix 1 and 2). Opportunities will be given for follow up questions prior to seeking study consent. Consent will be obtained for the baseline survey (prior to hospital discharge) and 3-months and 12-months follow up. For the follow ups, prior consent will be sought for the surveys to be conducted by post or over the telephone. The consent form (supplementary file, appendix 3 and 4) will have an option for the participants to only participate in a postal follow-up survey. Enrolment in the study will only occur if informed consent is obtained. Consenting family members will not be recruited if the patient declines to participate, as it will not be possible to gather patient demographic data without patient consent. Those enrolled will also be encouraged to contact the principal researcher at any time if they need further clarification on any aspects of the study.

The initial (baseline) assessments with consenting patients and families will be made after ICU discharge, while the patients are still in hospital using validated screening tools as described below. Patient and family member contact details (name, mailing address, contact numbers) will be collected to enable contact for the 3 and 12 months assessments. If a participant is lost to follow-up at 3-months, they will be continued to be included in the study until the next follow-up at 12-months. Participants will be considered to be lost to follow-up if neither the 3 or 12-month follow up data is available. Hospital databases will be screened to obtain information to confirm their discharge from hospital and any recorded death of the patients before attempting to contact the participants. In the event of a recorded patient death, no attempt will be made to contact participating families in an attempt to avoid distress. If the patient or the family member revoke consent, they will be withdrawn from the study and neither the patient nor the family member will be approached about the study.

Assessment tools:

Figure 1 shows the planned assessment tools and intervals for data collection with details of the screening tools to be used as follows.

Post-Traumatic Stress Syndrome 14 (PTSS-14) is a screening tool to identify patients at risk of suffering PTSD in ICUs. The UK-PTSS-14 (35) is a 14-item self-report screening tool; each item is rated 1 (never) to 7 (always) with a total score ranging from 14 to 98 (supplementary file, appendix 5).

Impact of Event Scale – Revised (IES-R), has 22 questions to better capture the DSM-IV criteria for PTSD (36) (supplementary file, appendix 6). The tool, not diagnostic for PTSD, is an appropriate instrument to measure the subjective response to a specific traumatic event, especially in the response sets of intrusion (intrusive thoughts, nightmares, intrusive feelings and imagery, dissociative-like re-experiencing), avoidance (numbing of responsiveness, avoidance of feelings, situations, and ideas), and hyperarousal (anger, irritability, hypervigilance, difficulty concentrating, heightened startle).

Depression and Anxiety Stress Scales - 21 (DASS-21) is a screening tool for identifying, differentiating and assessing depression, anxiety, and stress (37). DASS-21 consists of 7 items per scale. DASS allows a way to measure the severity of a patient's core symptoms related to depression, anxiety and stress (supplementary file, appendix 7).

All the above screening tools are short self-administered scales, each taking about 3 to 5 minutes to administer which will not overtire patients who could still be weak.

The prevalence of PTSD will be obtained by using the PTSS-14 in ICU survivors and IES-R in the family members. To screen for anxiety and depression, DASS-21 tool will be administered to survivors and their family members. In addition to the above tools at 3 and 12 months follow up, the ICU patient survivors and family members will be assessed for their health-related quality of life using the EQ-5D-5L questionnaire at the time of 3 and 12-month follow-up (supplementary file, appendix 8).

The lead investigator has obtained permission to use questionnaires for the study via e-mail correspondence with Dr Emma Twigg (PTSS-14), Prof Daniel Weiss (IES-R); EuRoQol Research Foundation (EQ-5D-5L) and the DASS-21 tool is freely available.

Managing participant distress: In general terms, the investigators will deal with the participant distress by using the LAST approach –

Listen to concerns
Acknowledge participant's distress
Support them by first apologizing for raising the matter with them and then provide information about seeking appropriate counselling (as detailed above)
Thanking the participants for their involvement in the study to date.

In the case of distress in study participants at the time of the telephone survey,

trained ICU research staff will enact the above protocol and the study investigators will attempt to make contact with the participant within 72 hours, to ensure their well-being of the study participant. At this time, the distressed participants will be advised to see their General Practitioner, and they will be re-provided with the contact details of their local mental health services should they require their help. Further, they will be offered the opportunity to have the investigators organize this contact for them, if they so wish.

Study participants will not immediately be excluded from the study at this stage, as they may feel that they will benefit from the increased oversight provided by the study. However, they will be asked directly if they still want to continue in the study. In the case of a refusal to continue with the study, the participants will be excluded from any further contact by the ICU research staff.

Data collection

Screening log:
A screening log will be maintained to identify reasons for non-recruitment and withdrawal of consent.

Baseline data:
Once consent is obtained, retrospective chart data will be collected as follows:

- Demographic data at the time of ICU admission [age, sex, Acute Physiology And Chronic Health Evaluation (APACHE) II Score, APACHE III Diagnosis, type of ICU admission [trauma/emergency surgical/medical])
- Duration and type of mechanical ventilation in ICU (invasive/non-invasive)
- Types of sedative drugs used during ICU stay, especially use of benzodiazepines and dexmedetomidine
- Record of routine sedation scores used in the participating ICU (if any)
- Record of delirium assessment by Confusion Assessment Method for the ICU scale - CAM-ICU (if available) during their ICU stay
- Review of new onset antipsychotic medications administered in the ICU (haloperidol, olanzapine, risperidone, quetiapine)
- Cumulative fluid balance during ICU stay
- Length of ICU stay
- Length of hospital stay
- Discharge destination from ICU and hospital (home/rehabilitation hospital/nursing home)

Data management and statistical analysis plan
The confidentiality of the participant data will be maintained unless disclosure is required by law. Participants will not be identified by name, and confidentiality of the information derived from medical records will be preserved. All data, including paper-based Contact Report Form (CRF) will be stored securely. Electronic database will be maintained on a password-protected computer maintained on secure government servers.

Power:

The primary aim of the study is to characterise the long term psychological outcomes (affective symptoms) in Australian intensive care survivors and family members. The study investigators performed a power calculation to compare the difference in prevalence between the intubated and non-intubated group. A sample size of 62 patients in the intubated group and 62 in the non-intubated group will provide 80% power to detect a statistically significant difference between the two groups, with an underlying prevalence of post-ICU affective symptom estimate of 30% and 10% in the intubated and non-intubated populations, respectively, using chi-square tests at a significance level of 5%. The estimate rates for the populations was based on literature review as described below. Based on literature, a potential attrition rate of 20% will be used for the 3 and 12 months follow up and hence the study will plan to recruit 150 participants (75 patients and 75 family members) in each of the groups (13,38,39). Sample size calculations were performed using Stata version 12.1.
The prevalence of affective symptoms in ICU survivors varies widely between studies based on the screening assessment tools. An assumed prevalence of 30% in the study group was based upon a broad literature review. The review by Davydow et al across several studies revealed a median point prevalence of substantial questionnaire- ascertained substantial PTSD symptoms of 22%(25). In another review by Davydow et al, the median point prevalence of substantial PTSD symptoms in Acute Respiratory Distress Syndrome survivors was 28% (19). In a recent review, Myrhen et al showed that a significant proportion of the patients (26.9%) had severe PTSD-related symptoms (38). The incidence of depressive symptoms in ICU survivors has also been noted to be between 28- 30% (22,39).
The prevalence of psychological/emotional stress varies in the family members of ICU survivors. The incidence of anxiety, PTSD and depression among family members of ICU survivors is high at the time of the ICU admission of their loved ones, but this decreases post discharge, and is variably quoted between 20 - 40% in various studies (28,29,32,40). There is no specific literature related to psychological outcomes in non-intubated ICU patients. Australian population prevalence rates for PTSD are approximately 5% and 10% for anxiety and depression (41, 42). Hence a composite estimate of 10% was used for the non-intubated group.

Statistical analysis plan:
Patient demographic and baseline characteristics in the two patient cohorts will be summarised using means, standard deviations, medians, and 25-75% quartiles for the continuous measures, and frequencies and percentages for categorical measures. ICU patient survivor outcomes (PTSS-14 and DASS-21) at baseline and at 3 and 12 months follow-up will be compared between the groups using a mixed model analysis. A time by group interaction will be tested. Means and standard errors for PTSS-14 and DASS-21 scores for each time period and risk group will be presented and compared. ICU patient family members outcomes using IES-R and DASS-21 will be analysed similarly. The EQ-5D-5L evaluates HRQoL using 5-point intensity rating scales ranging from “none” to “severe”, with high scores indicating severe issues in the domain. Once the total score has been summed, an algorithm will be used to convert the score, consistent with the approach used by the scale authors. Index scores will then be compared to a UK dataset, as advised and confirmed by email correspondence with the EQ-5D-5L authors (EuroQoL group). Multivariate analysis will be used to look for association between ICU survivors and family members. All analysis will be two-tailed, and p-values less than 0.05 will be

considered statistically significant. All analyses will be performed using SPSS version 22.

Ethics and dissemination

The study is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12615000880549).

This study will be performed in accordance with the ethical principles of the Declaration of Helsinki and National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Research Involving Humans (March, 2007). The principal investigator will ensure adherence to these guidelines. The study investigators are responsible for obtaining ethics approval from their individual state and territory HRECs. Individual hospitals will obtain approval from their local site-specific governance committees. Amendments to the study protocol will be submitted for ethical approval.

The results of this study will be published in a peer-reviewed medical journal and presented to the local intensive care community and other stakeholders.

Authors' contribution

SR is the chief investigator of the multicenter study, PRICE.
SR, RB, IM wrote the first draft of the manuscript.
SR, RB, FVH, TN, KS, AR, IM all contributed to the study design.
SR, IM were co-applicants on the ACT Health Private Practice Fund grant.
KS, SR were co-applicants on the Maurice Sando Foundation Sponsorhip Scheme.
All authors have critically evaluated and approved the manuscript.

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Competing interests

None declared.

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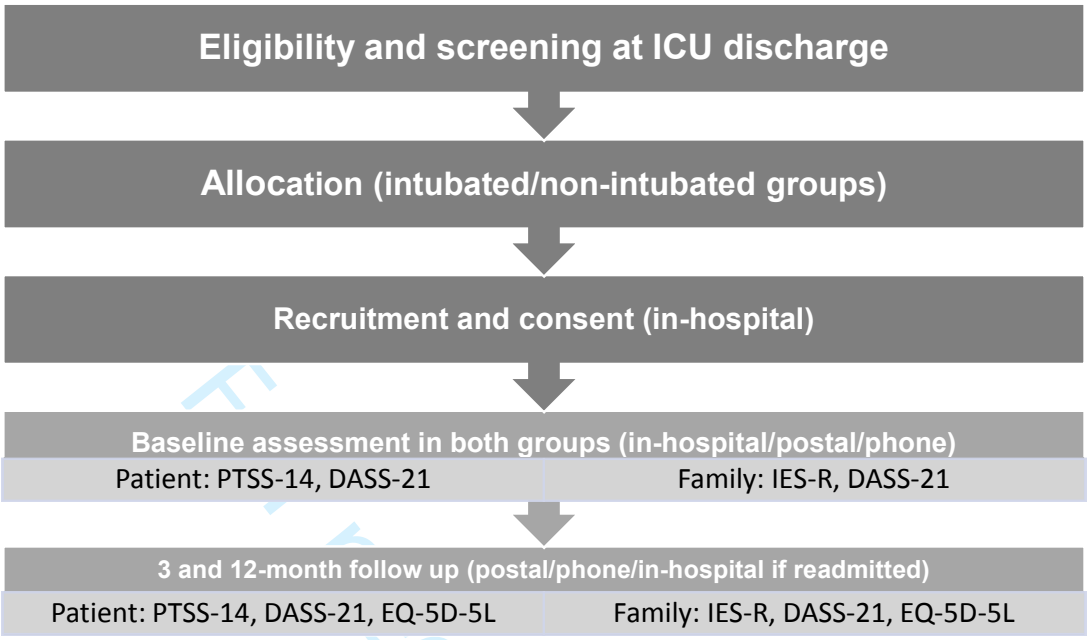


Figure 1: Assessment tools and follow-up intervals

PTSS-14: Post-Traumatic Stress Syndrome-14 intensive care screening tool
DASS-21: Depression and Anxiety Stress Scales - 21
IES-R: Impact of Event Scale - Revised
EQ-5D-5L: 5-level health related quality of life tool (EuroQol group)

Appendix 1

PATIENT INFORMATION SHEET

Psychological stRess in Intensive CarE survivors (PRICE study)

Invitation

You are invited to participate in a research study being conducted by the _____ Intensive Care Unit (ICU) looking at the incidence of psychological symptoms in patients who have been admitted to the ICU. We will also study the incidence of psychological symptoms in families of intensive care patients.

Critically ill patients requiring support in ICU may take a minimum of 6-12 months to physically get back to what is normal for them. In addition, recent literature suggests that some patients who survive intensive care unit are likely to have some psychological symptoms. Although this may relate to the critical nature of the illness itself, but also to some of the treatment necessitating recovery, e.g. sedation, breathing machines (ventilators), etc.

1. What is the purpose of this study?

To screen ICU patients for psychological symptoms after their discharge from ICU. This study will follow up intensive care patients up to 12 months post discharge from ICU. This knowledge will assist in deepening understanding of the long term impact of ICU thus facilitating strategies, prevention and treatment of these psychological symptoms.

2. Who is conducting this study?

The research team at the Intensive Care Unit of the _____Hospital is conducting the study.

3. Why have I been invited to participate in this study?

As a critically ill patient who was admitted to the intensive care unit for organ support, you are eligible to participate in the study.

4. What if I don't want to take part in this study or if I want to withdraw later?

Participation in this study is voluntary and your decision will not affect the medical management. If you wish to withdraw from the study you can do so at any time without justifying your decision. If you do withdraw from the study, all of the data already collected about you as part of the study will be destroyed and no data or information collected will be used in anyway by the researchers or sent outside this

institution. No additional information will be collected for the purposes of this study and you will not be contacted again.

5. What does this study involve?

Participation in this study involves allowing the study investigators to access your medical records and to be involved in 3 short surveys after your discharge from ICU. An initial survey will be done in hospital after ICU discharge. One of the research investigators will meet you while you are still in hospital. A follow up survey will be done at 3 and 12 months after discharge. This will be in the form of either a postal or a telephonic interview answering a short series of questions. This will assist us to determine if there have been any changes during that time.

We will be using a set of screening tools (questionnaire) called Post Traumatic Stress Scale (PTSS-14); Impact of Events Scale-Revised (IES-R); Depression Anxiety Stress Scales (DASS 21). These tools measure some of the symptoms you may be experiencing as a result of being through a traumatic event of being admitted to intensive care. In addition, we would be assessing the impact of hospitalisation on your quality of life using a validated tool called EQ-5D

6. Will my taking part in this study be kept confidential?

You have the right to privacy and all information that is collected during this study is confidential to the extent permitted by the applicable laws and regulations. Your study data will be made anonymous by the assignment of a unique number to you alone. All data collected from you will then be identified by this number. No data which could be used to identify you will be transferred from your medical notes.

The medical information collected during this study will then be transferred into study database(s) and processed to allow the results of this study to be analysed and reported or published for scientific purposes. Paper records including contact information will be stored in locked rooms accessible only to authorized study personnel. Electronic information will be kept on password-protected computers accessible only to authorized study personnel.

Your identity will be kept confidential at all times. Your personal information will only be disclosed with your permission, except as required by law.

7. Are there risks to me in taking part in this study?

No questions will be asked of you about any specific instances or memories of your time in the ICU. However, it is possible that you may experience some discomfort or distress as you may recollect some unpleasant memories from your stay in intensive care. Participation in the study will ensure that distress can be potentially diagnosed and appropriate referral made. In the unlikely event that you do feel distressed by any of the questions, we would encourage you to discuss any concerns with the study coordinator or your General Practitioner.

8. Will I benefit from the study?

This study aims to look at the psychological impact of ICU stay and gain further medical knowledge. This study may help to improve treatment for others with similar conditions, and the results of the study will be published in a major international medical journal. You may not receive any direct benefits from this research.

9. Will taking part in this study cost me anything, and will I be paid?

Participation in this research study will not cost you anything. You will not be paid or receive any financial benefits from taking part in this research study.

10. What happens with the results?

The results obtained will be collated and published in medical journals, conference presentations and other professional forums. In any publication, information will be provided in such a way that you cannot be identified. Results of the study will be provided to you, if you wish.

11. What should I do if I want to discuss this study further before I decide?

When you have read this information, the study investigator will discuss it with you and clarify any queries you may have. If you would like to know more at any stage, please do not hesitate to contact _____ on _____, or study coordinator _____ on _____.

12. Who can I contact if I have any questions or problems?

For questions about the study you can contact the principal investigator, Dr _____ on _____or email _____. You may also contact the site research coordinator, _____ on _____ or email at _____

If you find that any of the research questions are distressing to you, please do not continue with the study. There are services to help you. Please talk to your GP, or contact one of the services below:

- Lifeline (24 Hours): 13 11 14 - www.lifeline.org.au
- ACT Health (Crisis Team): 1800 629 354 or (02) 6205 1065
- NSW Mental Health Line: 1800 011 511
- Beyond blue (24 Hours): 1300 224 636 - www.beyondblue.org.au
- SANE (9:00am - 5:00pm): 1800 187 263 - www.sane.org
- Suicide Callback Service (24 Hours): 1300 659 467 - www.suicidecallbackservice.org.au

13. Who should I contact if I have concerns about the conduct of this study?

This study has been approved by _____ Health Human Research and Ethics Committee. Any concerns or complaints about the conduct of this study can be directed to the _____ Health Directorate Human Research Ethics Committee Secretariat, on _____ or via email _____

Thank you for taking the time to consider this study.
If you wish to continue to take part in it, please sign the attached consent form.
This information sheet is for you to keep.

Appendix 2

FAMILY MEMBER/NEXT OF KIN INFORMATION SHEET

Psychological StRess in Intensive CarE Survivors (PRICE study)

Invitation

You are invited to participate in a research study being conducted by the _____ Hospital Intensive Care Unit (ICU) looking at the incidence of psychological symptoms in close family members of patients who have been admitted to the ICU. We will also study the incidence of psychological symptoms in intensive care patients.

Critically ill patients requiring support in ICU may take a minimum of 6-12 months to physically get back to what is normal for them. It has become apparent that ICU relatives are also traumatised by their ICU experience and can sometimes show high levels of psychological symptoms. This study is being conducted to look for the incidence of such symptoms.

1. What is the purpose of this study?

To screen families/next of kin of ICU patients for psychological symptoms after their stay in ICU. Participants in the study will be followed up to 12 months post discharge from ICU. This knowledge will assist in deepening understanding of the long term impact of ICU thus facilitating strategies, prevention and treatment of psychological symptoms.

2. Who is conducting this study?

The research team at the Intensive Care Unit of the _____ Hospital is conducting the study.

3. Why have I been invited to participate in this study?

You are the family member/next of kin (NOK) of a critically ill patient who is admitted to intensive care needing organ support This makes you eligible to participate in the study.

4. What if I don't want to take part in this study or if I want to withdraw later?

Participation in this study is voluntary and your decision will not affect the medical management of your loved one. If you wish to withdraw from the study, you can do so at any time without justifying your decision. If you do withdraw from the study, all of the data already collected about you as part of the study will be destroyed and no data or information collected will be used in anyway by the researchers or sent

outside this institution. No additional information will be collected for the purposes of this study and you will not be contacted again.

5. What does this study involve?

Participation in this study involves 3 short surveys after the discharge of your loved one from ICU. An initial survey will be done in hospital after ICU discharge. One of the research investigators will meet you while you are still in hospital. Follow up surveys will be done at 3 and 12 months after discharge. This will be in the form of either a postal or a telephonic interview answering a short series of questions. This will assist us to determine if there have been any changes during that time.
Families/next of kin will be responding to a Revised Impact of Event Scale (IES-R) & Depression Anxiety Score Scale-21 (DASS-21). These tools measure the level of distress you may be experiencing as a result of your loved one being admitted to intensive care. In addition, we would be assessing the impact of your family members' hospitalisation on your quality of life using a validated tool called EQ-5D

6. Will my taking part in this study be kept confidential?

You have the right to privacy and all information that is collected during this study is confidential to the extent permitted by the applicable laws and regulations. Your study data will be made anonymous by the assignment of a unique number to you alone. All data collected from you will then be identified by this number.
Paper records including contact information will be stored in locked rooms accessible only to authorized study personnel. Electronic information will be kept on password-protected computers accessible only to authorized study personnel.
Your identity will be kept confidential at all times. Your personal information will only be disclosed with your permission, except as required by law.

7. Are there risks to me in taking part in this study?

No questions will be asked of you about any specific instances or memories of the time your loved one was admitted in the ICU. However, it is possible that you may experience some discomfort or distress as you may recollect some unpleasant memories from that time. Participation in the study will ensure that distress can be potentially diagnosed and appropriate referral made. In the unlikely event that you do feel distressed by any of the questions, we would encourage you to discuss any concerns with the study coordinator or your General Practitioner.

8. Will I benefit from the study?

This study aims to look at the psychological impact of ICU stay and gain further medical knowledge. This study may help to improve support for others with similar experiences, and the results of the study will be published in a major international medical journal. You may not receive any direct benefits from this research.

9. Will taking part in this study cost me anything, and will I be paid?

Participation in this research study will not cost you anything. You will not be paid or receive any financial benefits from taking part in this research study.

10. What happens with the results?

The results obtained from de-identified data will be collated and published in medical journals, conference presentations and other professional forums. In any publication, information will be provided in such a way that you cannot be identified. Results of the study will be provided to you, if you wish.

11. What should I do if I want to discuss this study further before I decide?

When you have read this information, the study investigator will discuss it with you and clarify any queries you may have. If you would like to know more at any stage, please do not hesitate to contact _____ on _____, or study coordinator _____ on _____.

12. Who can I contact if I have any questions or problems?

For questions about the study you can contact the principal investigator, Dr _____ on _____ or email _____. You may also contact the site research coordinator, _____ on _____ or email at _____

If you find that any of the research questions are distressing to you, please do not continue with the study. There are services to help you. Please talk to your GP, or contact one of the services below:

- Lifeline (24 Hours): 13 11 14 - www.lifeline.org.au
- ACT Health (Crisis Team): 1800 629 354 or (02) 6205 1065
- NSW Mental Health Line: 1800 011 511
- Beyond blue (24 Hours): 1300 224 636 - www.beyondblue.org.au
- SANE (9:00am - 5:00pm): 1800 187 263 - www.sane.org
- Suicide Callback Service (24 Hours): 1300 659 467 - www.suicidecallbackservice.org.au

13. Who should I contact if I have concerns about the conduct of this study?

This study has been approved by _____ Health Human Research and Ethics Committee. Any concerns or complaints about the conduct of this study can be directed to the _____Health Directorate Human Research Ethics Committee Secretariat, on _____ or via email _____.

Thank you for taking the time to consider this study.
If you wish to continue to take part in it, please sign the attached consent form.
This information sheet is for you to keep.

Appendix 3

Psychological stRess in Intensive CarE survivors (PRICE Study)

Patient Consent Form

I, _____(Full name of patient) of _____(address), have been explained about the study and have been asked to consent to participate in a research project entitled: PRICE: Psychological stRess in Intensive CarE survivors

In relation to this study I have read the Patient Information Sheet and have been informed of the following points:

1. Approval has been given by the _____ Health Directorate Human Research Ethics Committee. The aim of the study is to investigate cognitive and psychosocial function of patients who are critically ill and mechanically ventilated in Intensive Care Unit (ICU).
2. The results obtained from the study will not be of direct benefit to my medical management.
3. The study procedure will involve an initial assessment immediately after ICU discharge and 2 follow up surveys up to 12 months after ICU discharge.
4. I consent to being surveyed via post/telephone/both (strike out which is not applicable), as explained in the Study Information Sheet.
5. Possible adverse effects or risks related to this study may include potentially experiencing discomfort as a result of reflecting on the experience in ICU. I am aware that in this case I will be offered psychological assistance.
6. I understand that I have the ability to withdraw consent and therefore participation in the study at any stage. I am also aware that this will not in any way jeopardise my present or future care, or my relationship with the hospital.
7. Should I develop a problem which I suspect may have resulted from my involvement in this project, I am aware that I may contact the study principal investigator, Dr _____ on _____ or email at _____.
8. Should I have any problems or queries about the way in which the study was conducted, and I do not feel comfortable contacting the study staff, I am aware that I may contact the _____ Health Directorate Human Research Ethics Committee Secretariat, on _____ or via email _____
9. Participation in this project will not result in any extra medical or hospital costs to either my partner/friend/relative or I.
10. I understand that while the results of the research will be made accessible, my involvement and the identity will not be revealed.

11. In giving my consent, I acknowledge that the relevant Health Department Officials and the staff directly involved in the study may examine my medical records only as they relate to this project.
12. There is no foreseeable injury as a result of participating in this study; therefore any compensation will not be applicable.

After considering all these points, I accept the invitation to participate in this study.

Name: _____Date: _____
Signature _____
Investigator (Name): _____Date: _____
Signature (Investigator) _____

REVOCATION OF CONSENT

PRICE: Psychological stRess in Intensive CarE survivors

I hereby wish to WITHDRAW my consent to participate in the study described above and understand that such withdrawal WILL NOT jeopardise any treatment or my relationship with my health care providers.

Signature Date

Please PRINT Name _____

Appendix 4

Psychological stRess in Intensive CarE survivors (PRICE Study)

Family members' consent form

I, _____(Full name) of _____(address), have been explained about the study and have been asked to consent to participate in a research project entitled: PRICE: Psychological stress in intensive care survivors

In relation to this study I have read the Information Sheet and have been informed of the following points:

1. Approval has been given by the _____ Health Directorate Human Research Ethics Committee. The aim of the study is to investigate the psychological effect of a stay in the ICU.
2. The results obtained from the study will not be of direct benefit to my loved one's medical management.
3. The study procedure will involve an initial assessment immediately after ICU discharge and 2 follow up surveys till 12 months.
4. I consent to being surveyed via post/telephone/both (strike out which is not applicable), as explained in the Study Information Sheet.
5. Possible adverse effects or risks related to this study may include potentially experiencing discomfort as a result of reflecting on the experience in ICU. I am aware that in this case I will be offered psychological assistance.
6. I understand that I have the ability to withdraw consent and therefore participation in the study at any stage. I am also aware that this will not in any way jeopardise the present or future care of my loved one, or my relationship with the hospital.
7. Should I develop a problem which I suspect may have resulted from my involvement in this project, I am aware that I may contact the study principal investigator, Dr _____ on _____ or email at _____.
8. Should I have any problems or queries about the way in which the study was conducted, and I do not feel comfortable contacting the study staff, I am aware that I may contact the _____Health Directorate Human Research Ethics Committee Secretariat, on _____ or via email _____.
9. Participation in this project will not result in any extra medical or hospital costs to either my partner/friend/relative or I.
10. I understand that while the results of the research will be made accessible, my involvement and the identity will not be revealed.

11. In giving my consent, I acknowledge that the relevant Health Department Officials and the staff directly involved in the study may examine my loved one's medical records only as they relate to this project.
12. There is no foreseeable injury as a result of participating in this study; therefore any compensation will not be applicable.

After considering all these points, I accept the invitation to participate in this study.

Name: _____Date: _____
Signature _____
Investigator (Name): _____Date: _____
Signature (Investigator) _____

REVOCATION OF CONSENT

PRICE: Psychological stress in intensive care survivors

I hereby wish to WITHDRAW my consent to participate in the study described above and understand that such withdrawal WILL NOT jeopardise any treatment of my loved one, or my relationship with my health care providers.

Signature Date

Please PRINT Name _____

Appendix 5

PTSS-14 Intensive Care Screen

This form should not take longer than about 5 minutes to complete. The form has two sections, Part A and Part B.

PART A

This consists of four statements about your memory of the time you spent on the Intensive Care Unit. Read each statement. If a statement is FALSE, tick the NO box. If the statement is TRUE, tick the YES box. Please answer ALL four questions. Tick only ONE box for each statement. If you make a mistake, simply cross out the wrong answer and tick the correct box.

PART B

This consists of 10 statements about how you have been feeling in the past few days. You need to decide HOW OFTEN you have been feeling this way in the past few days.

If you have NOT EVER felt or experienced what the statement says in the past few days, circle 1 (never).

If you have been feeling or experiencing it ALL THE TIME, circle 7 (always).

Otherwise, circle one of the numbers in between that best describes how much you have been feeling or experiencing what the statement says in the past few days.
Please circle only one number for each statement. If you make a mistake, simply cross it out and circle the correct number. PLEASE be sure to choose a number for ALL 14 statements.

A. When I think back to the time of my severe illness and the time I spent in the Intensive Care Unit (ICU), I remember:

Nightmares	No	☐	Yes	☐
Severe Anxiety or Panic	No	☐	Yes	☐
Severe Pain	No	☐	Yes	☐
Troubles to breath, feelings of suffocation	No	☐	Yes	☐

B. Presently (this means in the past few days) I suffer from:

1. sleep problems

never						always
1	2	3	4	5	6	7

2. nightmares

never						always
1	2	3	4	5	6	7

3. depression, I feel dejected/downtrodden

never always

1 2 3 4 5 6 7

4. jumpiness, I am easily frightened by sudden sounds or sudden movements

never always

1 2 3 4 5 6 7

5. the need to withdraw from others

never always

1 2 3 4 5 6 7

6. irritability, that is, I am easily agitated/annoyed and angry

never always

1 2 3 4 5 6 7

7. frequent mood swings

never always

1 2 3 4 5 6 7

8. a bad conscience, blame myself, have guilt feelings

never always

1 2 3 4 5 6 7

9. fear of places and situations, which remind me of the ICU

never always

1 2 3 4 5 6 7

10. muscular tension

never always

1 2 3 4 5 6 7

11. *upsetting, unwanted thoughts or images of my time on the ICU*

never always

1 2 3 4 5 6 7

12. *feeling numb (e.g. cannot cry, unable to have loving feelings)*

never always

1 2 3 4 5 6 7

13. *avoid places, people or situations that remind me of the ICU*

never always

1 2 3 4 5 6 7

14. feeling as if my plans or dreams for the future will not come true

never always

1 2 3 4 5 6 7

Appendix 6
IMPACT OF EVENT SCALE- REVISED

INSTRUCTIONS: Below is a list of difficulties people sometimes have after stressful life events. Please read each item, and then indicate how distressing each difficulty has been for you **DURING THE PAST SEVEN DAYS** with respect to _____, which occurred on _____. How much were you distressed or bothered by these difficulties?

Not at all = 0	A little bit = 1	Moderately = 2	Quite a bit = 3	Extremely = 4

1. Any reminder brought back feelings about it.
2. I had trouble staying asleep.
3. Other things kept making me think about it.
4. I felt irritable and angry.
5. I avoided letting myself get upset when I thought about it or was reminded of it.
6. I thought about it when I didn't mean to.
7. I felt as if it hadn't happened or wasn't real.
8. I stayed away from reminders of it.
9. Pictures about it popped into my mind.
10. I was jumpy and easily startled.
11. I tried not to think about it.
12. I was aware that I still had a lot of feelings about it, but I didn't deal with them.
13. My feelings about it were kind of numb.
14. I found myself acting or feeling like I was back at that time.
15. I had trouble falling asleep.
16. I had waves of strong feelings about it.
17. I tried to remove it from my memory.
18. I had trouble concentrating.
19. Reminders of it caused me to have physical reactions, such as sweating, trouble breathing, nausea, or a pounding heart.
20. I had dreams about it.
21. I felt watchful and on-guard.
22. I tried not to talk about it.

Citations: Weiss, D.S. & Marmar, C.R. (1997). The Impact of Event Scale-Revised. In J.P. Wilson, & T. M. Keane (Eds.), *Assessing Psychological Trauma and PTSD: A Practitioner's Handbook*. (pp. 399-411). New York: Guilford.
Weiss, D. S. (2004). The Impact of Event Scale-Revised. In J. P. Wilson, & T. M. Keane (Eds.), *Assessing psychological trauma and PTSD: A practitioner's handbook* (2nd ed., pp. 168-189). New York: Guilford Press.

Appendix 7

DASS21	*Name:*	*Date:*			

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you *over the past week*. There are no right or wrong answers. Do not spend too much time on any statement.

The rating scale is as follows:
0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of time
3 Applied to me very much, or most of the time

1	I found it hard to wind down	0	1	2	3
2	I was aware of dryness of my mouth	0	1	2	3
3	I couldn't seem to experience any positive feeling at all	0	1	2	3
4	I experienced breathing difficulty (eg, excessively rapid breathing, breathlessness in the absence of physical exertion)	0	1	2	3
5	I found it difficult to work up the initiative to do things	0	1	2	3
6	I tended to over-react to situations	0	1	2	3
7	I experienced trembling (eg, in the hands)	0	1	2	3
8	I felt that I was using a lot of nervous energy	0	1	2	3
9	I was worried about situations in which I might panic and make a fool of myself	0	1	2	3
10	I felt that I had nothing to look forward to	0	1	2	3
11	I found myself getting agitated	0	1	2	3
12	I found it difficult to relax	0	1	2	3
13	I felt down-hearted and blue	0	1	2	3
14	I was intolerant of anything that kept me from getting on with what I was doing	0	1	2	3
15	I felt I was close to panic	0	1	2	3
16	I was unable to become enthusiastic about anything	0	1	2	3
17	I felt I wasn't worth much as a person	0	1	2	3
18	I felt that I was rather touchy	0	1	2	3
19	I was aware of the action of my heart in the absence of physical exertion (eg, sense of heart rate increase, heart missing a beat)	0	1	2	3
20	I felt scared without any good reason	0	1	2	3
21	I felt that life was meaningless	0	1	2	3

Appendix 8

Health Questionnaire

English version for Australia

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

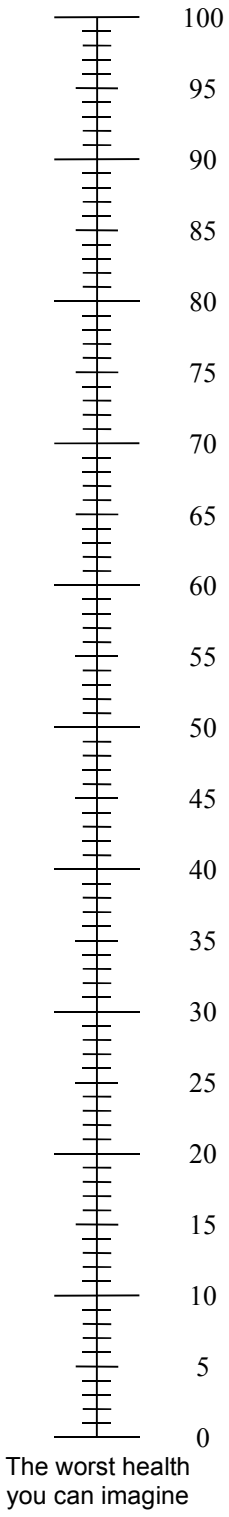
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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 ❑

- 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 = ☐



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Long-term follow up for Psychological stRess in Intensive CarE survivors (PRICE): study protocol for a multicentre, prospective observational cohort study in Australian intensive care units

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Long-term follow up for Psychological stRess in Intensive CarE survivors (PRICE): study protocol for a multicentre, prospective observational cohort study in Australian intensive care units

Sumeet Rai, Rhonda Brown, Frank Van Haren, Teresa Neeman, Arvind Rajamani, Krishnaswamy Sundararajan, Imogen Mitchell

Author details:

Sumeet Rai: Intensivist[1], Clinical lecturer[2] and PhD doctoral candidate[2]

Rhonda Brown: Associate Professor[3]

Frank Van Haren: Intensivist[1], Adjunct Professor[4]

Teresa M Neeman: Statistical consultant[5]

Arvind Rajamani: Intensivist[6], Clinical Lecturer[7]

Krishnaswamy Sundararajan: Intensivist[8], Senior Clinical Lecturer[9]

Imogen Mitchell: Intensivist[1], Professor[2] & Dean[2]

1. Canberra Hospital Intensive Care Unit, Garran, Canberra, Australia
2. Australian National University Medical School, Canberra, Australia
3. Research School of Psychology, Australian National University, Canberra, Australia
4. University of Canberra, Bruce, Canberra, Australia
5. Statistical Consulting Unit, Australian National University, Canberra, Australia
6. Nepean Hospital, Kingswood, Sydney, Australia
7. University of Sydney, Sydney, Australia
8. Royal Adelaide Hospital, Adelaide, Australia
9. Discipline of Acute Care Medicine, University of Adelaide, Adelaide, Australia

Address for correspondence:

Sumeet Rai
Intensive Care Unit, Canberra Hospital, Yamba Drive, Garran, ACT, Canberra, Australia 2605
E-mail: Sumeet.Rai@act.gov.au

Keywords: intensive care, psychological, long-term outcomes

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Abstract

Introduction There are little published data on long-term psychological outcomes in intensive care unit (ICU) survivors and their family members in Australian ICUs. In addition, there is scant literature evaluating the effects of psychological morbidity in intensive care survivors on their family members. The aims of this study are to describe and compare the long-term psychological outcomes of intubated and non-intubated ICU survivors and their family members in an Australian ICU setting.

Methods and analysis This will be a prospective observational cohort study across four ICUs in Australia. The study aims to recruit 150 (75 intubated and 75 non-intubated) adult ICU survivors and 150 family members of the survivors from 2015-2018. Long-term psychological outcomes and effects on health-related quality of life (HRQoL) will be evaluated at 3 and 12 months follow up using validated and published screening tools. The primary objective is to compare the prevalence of affective symptoms in intubated and non-intubated survivors of intensive care and their families and its effects on HRQoL. The secondary objective is to explore dyadic relations of psychological outcomes in patients and their family members.

Ethics and dissemination The study has been approved by the relevant human research ethics committees (HREC) of Australian Capital Territory (ACT) Health (ETH.11.14.315), New South Wales (HREC/16/HNE/64), South Australia (HREC/15/RAH/346). The results of this study will be published in a peer-reviewed medical journal and presented to the local intensive care community and other stakeholders.

Trial registration number: Australian New Zealand Clinical Trials Registry (ACTRN12615000880549)

Strengths and limitations of this study:

Largest Australian long-term follow up study in intensive care survivors and family members.

Study includes non-intubated ICU patient population, as their outcomes have previously not been vigorously studied.

Study design includes dyads of ICU survivors and family members to explore interdependence of adverse outcomes.

The tools adopted to assess psychological and HRQoL outcomes are published and validated.

Significant limitation of the study design is the absence of pre-ICU admission data on health related quality of life, preventing comparisons with post-ICU outcomes.

Introduction

Over the last two decades, numerous long-term outcome studies have shown that survivors of critical illness can suffer from a complex myriad of health and socio-economic issues long after discharge from hospital (1-6). Initial seminal studies on long-term outcomes in critical illness are based on survivors of Acute Respiratory Distress Syndrome (ARDS), a condition traditionally treated with invasive ventilation, sedation and muscle relaxants (7-10). Long-term (1- to 5-years) outcomes of acute lung injury and ARDS survivors have been extensively studied (11,12) with emerging evidence of long-term follow-up outcomes in other categories of intensive care unit (ICU) survivors (3,13,14). The term “post intensive care syndrome” (PICS) was framed to describe new or worsening impairments in physical, cognitive, or mental health status developing after an episode of critical illness and persisting beyond discharge (15).

Based on the above research, it has been established, beyond reasonable doubt, that a significant proportion of ICU survivors experience long-term psychological consequences, including post-traumatic stress disorder (PTSD), anxiety and depression (16-20). The reported prevalence of adverse neuropsychiatric outcomes in intensive care survivors varies across studies. A recent systematic review of the literature from 2008 - 2012 suggests that up to 27% of ICU survivors suffer from PTSD(21). On the other hand, another recent study from the US found that the prevalence of PTSD in ICU survivors was 16% at 3 months post-ICU (22). A systematic review of the literature reveals that the reported prevalence of anxiety in ICU survivors ranges from 23% to 48% and 17% to 43% for depression (19). Another study shows an incidence of 31% for depressive symptoms post-ICU (22). Literature reviews suggests that severity of illness as evidenced by the need for intubation, mechanical ventilation and sedation are important risk factors for psychological stress in ICU survivors (23-26). However, there is very little literature on the incidence of psychological stress post ICU in the patients who do not need sedation, intubation and mechanical ventilation. Interventions to reduce PTSD in ICU survivors have excluded the less severe patient populations (not intubated and ventilated) (27). It is possible the incidence of psychological symptoms in such a population is low but this remains only a conjecture.

Published literature also suggests that a high proportion of family members of intensive care patients are left with varying psychological symptoms that can include anxiety, depression, and PTSD (28-31). Some of the possible precipitating factors impacting on the family’s psychological state include a concern for the nature of the patient's critical illness, perception of inadequate communication in the ICU, lack of adequate understanding of the patient’s illness, concerns about the patient’s prognosis, surrogate decision making on end of life care and the prospect of providing continuing care to survivors (29,32,33).

Family members and ICU survivors can essentially be considered a dyad and interactions between the dyads could have an influence on the physical and psychological health and health related quality of life outcomes of both (34). This emotional interdependence between ICU survivors and their spouses has been studied in a subset of adult sepsis and chronic critically ill survivors (35,36).

To date, there are little data from Australian ICUs about the prevalence of psychological stress in the ICU survivors and their family members. Drawing comparisons on prevalence rates across the continents from studies predominantly originating in America and Europe may not be helpful due to the variation in critical care services (37). In addition, emotional interdependence of dyads of ICU survivors and their family members have not been previously studied in a diverse group of ICU survivors and family members.

The primary aim of this multicentre study is to determine and compare the prevalence of affective symptoms in intubated and non-intubated ICU survivors and family members by screening them for PTSD, anxiety, depression and Health Related Quality of Life (HRQoL) over a 12-month follow up period. The secondary aims are to explore dyadic relations of psychological outcomes in patients and their family members.

We anticipate that the Psychological stRess in Intensive CarE survivors (PRICE) study will provide significant insight into the impact of affective symptoms on post intensive care survivors, especially the non-intubated group and their family members, as they have been previously excluded from studies. This will contribute to the existing body of knowledge, especially the interdependence between survivors and their family members.

Methods and analysis

Study design

PRICE is a multicentre, prospective, observational cohort study reviewing ICU survivors and their family members. The groups will be divided based on the following ICU admission characteristics:
a) Intubated group: Intubated ICU survivor and family member
b) Non-intubated group: Non-intubated ICU survivor and family member.

Setting

The study will be conducted in four Intensive Care Units in Australia: The Canberra Hospital, Australian Capital Territory; Nepean Hospital and John Hunter Hospital, New South Wales and Royal Adelaide Hospital, South Australia. All the four intensive care units are part of large public teaching hospitals. Local principal investigators, in conjunction with local research teams will conduct the trial in their respective hospitals. It is estimated that the study will take three years (2015-2018) to complete recruitment and follow up.

Study population

The study population will include adult (18 years and older) ICU survivors and their family members who have been discharged from ICU during the study period. Detailed inclusion and exclusion criteria are as follows:

ICU survivors:

Inclusion criteria:
A) Intubated ICU survivor:

- Able to provide valid, informed consent after ICU discharge

- Intubated and mechanically ventilated for more than 24 hours AND
- Stayed in intensive care unit for more than 72 hours

B) Non-intubated ICU survivor:
- Able to provide valid, informed consent after ICU discharge
- Not intubated during current ICU stay
- Received inotropic/vasopressor support and/or non-invasive ventilation during ICU stay

Exclusion criteria:
- Prior history of a psychiatric disorder/s in patient (psychotic disorders, chronic PTSD)
- Imminent death/palliative care patient (unlikely to be alive at follow up at 3, 12 months)
- Suspected acute primary brain lesion that may result in global impairment of consciousness or cognition, such as traumatic brain injury, intracranial haemorrhage, stroke, or hypoxic brain injury
- Unable to give informed consent prior to hospital discharge
- Non-English speaking background

Family Members:

Inclusion criteria:
- Family member (spouse/partner/next of kin/lives with patient normally) of a consenting ICU patient with above criteria
- Age 18 years and older

Exclusion criteria:
- Refusal of consent from the associated ICU survivor (as detailed below)
- Unable to give informed consent prior to hospital discharge
- Non-English speaking background

Patients will be screened for eligibility by the research staff in the participating ICUs after discharge from the ICU. Research staff will approach medical and nursing teams on the hospital wards to seek their permission to approach patients and also to confirm that the patients are not delirious and can provide appropriate consent. Absence of delirium will also be confirmed on reviewing the ward medical and nursing notes for the previous 24-48 hours before approaching the patients. Only patients with concerns about unresolved delirium in the hospital will be excluded.

Hospital records for patients will be checked for next of kin details and this will be confirmed from the patient. Patients and family members will be explained the study and provided with the appropriate study information sheet (supplementary file, appendix 1 and 2). Opportunities will be given for follow up questions prior to seeking study consent. The consent form (supplementary file, appendix 3 and 4) will have an option for the participants to only participate in a postal follow-up survey. Consenting patients included in the study will have follow-up assessments, even if family member declines to participate. Consenting family members will not be recruited if the patient declines to participate, as it will not be possible to gather patient demographic data without patient consent. Those enrolled will also be encouraged to

contact the principal researcher at any time if they need further clarification on any aspects of the study.

Follow-up:
The initial (baseline) assessments with consenting patients and families will be conducted in-hospital after ICU discharge, using validated screening tools as described below. Patient and family member contact details (name, mailing address, contact numbers) will be collected to enable contact for the 3 and 12 months assessments. If a participant is lost to follow-up at 3-months, they will continue to be included in the study until the next follow-up at 12-months. Participant follow-up will include postal and phone follow-up. Hospital databases will be screened to obtain information to confirm their discharge from hospital and any recorded death of the patients before attempting to contact the participants. In the event of a recorded patient death, no attempt will be made to contact participating families in an attempt to avoid distress. If hospital records indicate that the patient continues to be a hospital in-patient or has been readmitted to hospital during the designated follow-up time period, researchers will meet with them personally to check well-being and deliver the assessment tools. Participants will be considered lost to follow-up if neither 3 or 12-month follow up data is available. If the patient or the family member revoke consent, they will be withdrawn from the study and neither the patient nor the family member will be approached about the study again.

Figure 1 shows the planned assessment tools and intervals for data collection with details of the screening tools to be used as follows.

Screening tools:
Post-Traumatic Stress Syndrome 14 (PTSS-14) is a 14-item screening tool to identify patients at risk of suffering PTSD in ICUs (38,39). PTSS-14, although not a diagnostic tool, is a self-reporting screening tool; each item is rated 1 (never) to 7 (always) with a total score ranging from 14 to 98 (supplementary file, appendix 5).

Impact of Event Scale – Revised (IES-R), has 22 questions to better capture the DSM-IV criteria for PTSD (40,41) (supplementary file, appendix 6). The tool, not diagnostic for PTSD, is an appropriate instrument to measure the subjective response to a specific traumatic event, especially in the response sets of intrusion (intrusive thoughts, nightmares, intrusive feelings and imagery, dissociative-like re-experiencing), avoidance (numbing of responsiveness, avoidance of feelings, situations, and ideas), and hyperarousal (anger, irritability, hypervigilance, difficulty concentrating, heightened startle).

Depression and Anxiety Stress Scales - 21 (DASS-21) is a screening tool for identifying, differentiating and assessing depression, anxiety, and stress (42). DASS-21 consists of 7 items per scale. DASS allows a way to measure the severity of a patient's core symptoms related to depression, anxiety and stress (supplementary file, appendix 7). In addition, DASS has Australian normed values to draw comparison to.

All the above screening tools are short self-administered scales, each taking about 3 to 5 minutes to administer which will not overtire patients who could still be weak. Importantly, these screening tools are used to assess symptoms of affective

disorders and do not replace a clinician administered diagnostic interview, which needs significant time and professional expertise to complete.

The prevalence of PTSD symptoms will be obtained by using the PTSS-14 in ICU survivors and IES-R in the family members. To screen for anxiety and depression, DASS-21 tool will be administered to survivors and their family members. In addition to the above tools at 3 and 12 months follow up, the ICU patient survivors and family members will be assessed for their health-related quality of life using the EQ-5D-5L questionnaire (https://euroqol.org/wp-content/uploads/2016/10/Sample_UK__English__EQ-5D-5L_Paper_Self_complete_v1.0__ID_24700.pdf).

The lead investigator has obtained permission to use questionnaires for the study via e-mail correspondence with Dr Emma Twigg (PTSS-14), Prof Daniel Weiss (IES-R); EuRoQol Research Foundation (EQ-5D-5L), while the DASS-21 tool is freely available.

Managing participant distress: In general terms, the investigators will deal with participant distress using the LAST approach –

Listen to concerns
Acknowledge participant's distress
Support them by first apologizing for raising the matter with them and then provide information about seeking appropriate counselling
Thanking the participants for their involvement in the study to date.

In the case of distress in study participants at the time of the telephone survey, trained ICU research staff will enact the above protocol and the study investigators will attempt to make contact with the participant within 72 hours, to ensure their well-being of the study participant. At this time, the distressed participants will be advised to see their General Practitioner, and they will be re-provided with the contact details of their local mental health services should they require their help. Further, they will be offered the opportunity to have the investigators organize this contact for them, if they so wish.

Study participants will not immediately be excluded from the study at this stage, as they may feel that they will benefit from the increased oversight provided by the study. However, they will be asked directly if they still want to continue in the study. In the case of a refusal to continue with the study, the participants will be excluded from any further contact by the ICU research staff.

Data collection

Screening log:
A screening log will be maintained to identify reasons for non-recruitment and withdrawal of consent.

Baseline data:
Once consent is obtained, retrospective chart data will be collected as follows:

- Demographic data at the time of ICU admission [age, sex, Acute Physiology And Chronic Health Evaluation (APACHE) II Score, APACHE III Diagnosis, type of ICU admission [trauma/emergency surgical/medical])
- Duration and type of mechanical ventilation in ICU (invasive/non-invasive)
- Types of sedative drugs used during ICU stay, especially use of benzodiazepines and dexmedetomidine
- Record of routine sedation scores used in the participating ICU (if any)
- Record of delirium assessment by Confusion Assessment Method for the ICU scale - CAM-ICU or any other validated tool (if available) during their ICU stay
- Review of new onset antipsychotic medications administered in the ICU (haloperidol, olanzapine, risperidone, quetiapine)
- Cumulative fluid balance during ICU stay
- Length of ICU stay
- Length of hospital stay
- Discharge destination from ICU and hospital (home/rehabilitation hospital/nursing home)

Data management and statistical analysis plan

The confidentiality of the participant data will be maintained unless disclosure is required by law. Participants will not be identified by name, and confidentiality of the information derived from medical records will be preserved. All data, including paper-based Contact Report Form (CRF) will be stored securely. Electronic database will be maintained on a password-protected computer maintained on secure government servers.

Power:

The primary aim of the study is to characterise the long term psychological outcomes (affective symptoms) in Australian intensive care survivors and family members. The study investigators performed a power calculation to compare the difference in prevalence between the intubated and non-intubated group. A sample size of 62 patients in the intubated group and 62 in the non-intubated group will provide 80% power to detect a statistically significant difference between the two groups, with an underlying prevalence of post-ICU affective symptom estimate of 30% and 10% in the intubated and non-intubated populations, respectively, using chi-square tests at a significance level of 5%. The estimate rates for the populations was based on literature review as described below. Based on literature, a potential attrition rate of 20% will be used for the 3 and 12 months follow up and hence the study will plan to recruit 150 participants (75 patients and 75 family members) in each of the groups (13,43,44). Sample size calculations were performed using Stata version 12.1.
The prevalence of affective symptoms in ICU survivors varies widely between studies based on the screening assessment tools. An assumed prevalence of 30% in the study group was based upon a broad literature review. The review by Davydow et al across several studies revealed a median point prevalence of substantial questionnaire- ascertained substantial PTSD symptoms of 22%(25). In another review by Davydow et al, the median point prevalence of substantial PTSD symptoms in Acute Respiratory Distress Syndrome survivors was 28% (19). In a recent review, Myrhen et al showed that a significant proportion of the patients (26.9%) had severe PTSD-related symptoms (43). The incidence of depressive symptoms in ICU survivors has also been noted to be between 28- 30% (22,44).

The prevalence of psychological/emotional stress varies in the family members of ICU survivors. The incidence of anxiety, PTSD and depression among family members of ICU survivors is high at the time of the ICU admission of their loved ones, but this decreases post discharge, and is variably quoted between 20 - 40% in various studies (28,29,32,45). There is no specific literature related to psychological outcomes in non-intubated ICU patients. Australian population prevalence rates for PTSD are approximately 5% and 10% for anxiety and depression (46,47). Hence a composite estimate of 10% was used for the non-intubated group.

Statistical analysis plan:
Patient demographic and baseline characteristics in the two patient cohorts will be summarised using means, standard deviations, medians, and 25-75% quartiles for the continuous measures, and frequencies and percentages for categorical measures. ICU patient survivor outcomes (PTSS-14 and DASS-21) at baseline and at 3 and 12 months follow-up will be compared between the groups using a mixed model analysis. A time by group interaction will be tested. Means and standard errors for PTSS-14 and DASS-21 scores for each time period and risk group will be presented and compared. ICU patient family member outcomes using IES-R and DASS-21 will be analysed similarly. The EQ-5D-5L evaluates HRQoL using 5-point intensity rating scales ranging from “none” to “severe”, with high scores indicating severe issues in the domain. Once the total score has been summed, an algorithm will be used to convert the score, consistent with the approach used by the scale authors. Index scores will then be compared to a UK dataset, as advised and confirmed by email correspondence with the EQ-5D-5L Research Foundation. For the purposes of the primary outcome, missing data would be ignored.

Associations in the prevalence of affective disorders between patient and their family members will be explored using a modification of an actor-partner-interdependence model. In particular, the plan is to model the probability of affective disorders amongst patients and family members at 3 and 12 months using a multilevel generalised mixed model, using a nested variance structure with family unit as a random effect, and family member nested within family unit. Covariates of interest will include the affective disorder status of patient/family members at the preceding time, as well as patient characteristics e.g. intubation status.

All analysis will be two-tailed, and p-values less than 0.05 will be considered statistically significant. All analyses will be performed using SPSS version 22.

Patient and Public Involvement

The PRICE study protocol was reviewed by the local human research ethics committees (HREC), which routinely have community and consumer representatives. Protocol review by HREC involved community views and feedbacks, which contributed to the final study protocol. Patients were not involved in the recruitment and conduct of the study. Where requested, results will be disseminated to the study participants in the form of a published manuscript.

Ethics and dissemination

The study is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12615000880549).

This study will be performed in accordance with the ethical principles of the Declaration of Helsinki and National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Research Involving Humans (March, 2007). The principal investigator will ensure adherence to these guidelines.
The study has been approved by the relevant human research ethics committees (HREC) of Australian Capital Territory (ACT) Health (ETH.11.14.315), New South Wales (HREC/16/HNE/64), South Australia (HREC/15/RAH/346). Individual hospitals will obtain approval from their local site-specific governance committees.
Amendments to the study protocol will be submitted for ethical approval.

The results of this study will be published in a peer-reviewed medical journal and presented to the local intensive care community and other stakeholders.

Authors' contribution
SR is the chief investigator of the multicentre study, PRICE.
SR, RB, IM wrote the first draft of the manuscript.
SR, RB, FVH, TN, KS, AR, IM all contributed to the study design.
SR, IM were co-applicants on the ACT Health Private Practice Fund grant.
KS, SR were co-applicants on the Maurice Sando Foundation Sponsorship Scheme.
All authors have critically evaluated and approved the manuscript.

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Competing interests
None declared.

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Figure 1: Assessment tools and follow-up intervals

PTSS-14: Post-Traumatic Stress Syndrome-14 intensive care screening tool
DASS-21: Depression and Anxiety Stress Scales - 21
IES-R: Impact of Event Scale - Revised
EQ-5D-5L: 5-level health related quality of life tool (EuroQol group)

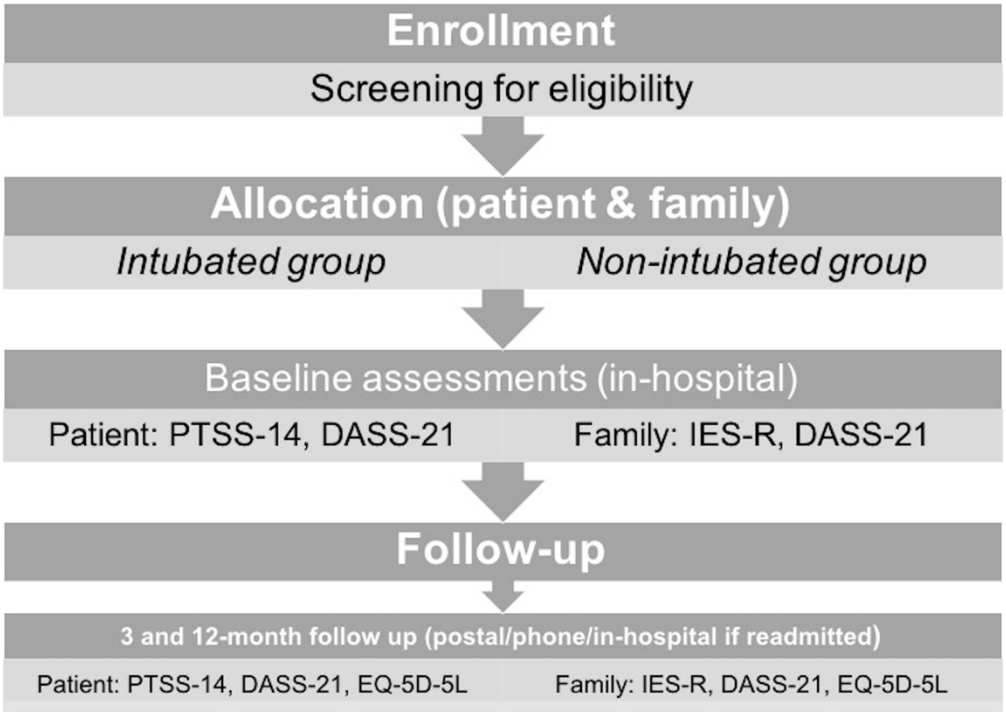

Figure 1: Assessment tools and follow-up intervals

PTSS-14: Post-Traumatic Stress Syndrome-14 intensive care screening tool
DASS-21: Depression and Anxiety Stress Scales - 21
IES-R: Impact of Event Scale - Revised
EQ-5D-5L: 5-level health related quality of life tool (EuroQol group)

184x132mm (300 x 300 DPI)

Appendix 1

PATIENT INFORMATION SHEET

Psychological stRess in Intensive CarE survivors (PRICE study)

Invitation

You are invited to participate in a research study being conducted by the _____ Intensive Care Unit (ICU) looking at the incidence of psychological symptoms in patients who have been admitted to the ICU. We will also study the incidence of psychological symptoms in families of intensive care patients.

Critically ill patients requiring support in ICU may take a minimum of 6-12 months to physically get back to what is normal for them. In addition, recent literature suggests that some patients who survive intensive care unit are likely to have some psychological symptoms. Although this may relate to the critical nature of the illness itself, but also to some of the treatment necessitating recovery, e.g. sedation, breathing machines (ventilators), etc.

1. What is the purpose of this study?

To screen ICU patients for psychological symptoms after their discharge from ICU. This study will follow up intensive care patients up to 12 months post discharge from ICU. This knowledge will assist in deepening understanding of the long term impact of ICU thus facilitating strategies, prevention and treatment of these psychological symptoms.

2. Who is conducting this study?

The research team at the Intensive Care Unit of the _____Hospital is conducting the study.

3. Why have I been invited to participate in this study?

As a critically ill patient who was admitted to the intensive care unit for organ support, you are eligible to participate in the study.

4. What if I don't want to take part in this study or if I want to withdraw later?

Participation in this study is voluntary and your decision will not affect the medical management. If you wish to withdraw from the study you can do so at any time without justifying your decision. If you do withdraw from the study, all of the data already collected about you as part of the study will be destroyed and no data or information collected will be used in anyway by the researchers or sent outside this

institution. No additional information will be collected for the purposes of this study and you will not be contacted again.

5. What does this study involve?

Participation in this study involves allowing the study investigators to access your medical records and to be involved in 3 short surveys after your discharge from ICU. An initial survey will be done in hospital after ICU discharge. One of the research investigators will meet you while you are still in hospital. A follow up survey will be done at 3 and 12 months after discharge. This will be in the form of either a postal or a telephonic interview answering a short series of questions. This will assist us to determine if there have been any changes during that time.

We will be using a set of screening tools (questionnaire) called Post Traumatic Stress Scale (PTSS-14); Impact of Events Scale-Revised (IES-R); Depression Anxiety Stress Scales (DASS 21). These tools measure some of the symptoms you may be experiencing as a result of being through a traumatic event of being admitted to intensive care. In addition, we would be assessing the impact of hospitalisation on your quality of life using a validated tool called EQ-5D

6. Will my taking part in this study be kept confidential?

You have the right to privacy and all information that is collected during this study is confidential to the extent permitted by the applicable laws and regulations. Your study data will be made anonymous by the assignment of a unique number to you alone. All data collected from you will then be identified by this number. No data which could be used to identify you will be transferred from your medical notes.

The medical information collected during this study will then be transferred into study database(s) and processed to allow the results of this study to be analysed and reported or published for scientific purposes. Paper records including contact information will be stored in locked rooms accessible only to authorized study personnel. Electronic information will be kept on password-protected computers accessible only to authorized study personnel.

Your identity will be kept confidential at all times. Your personal information will only be disclosed with your permission, except as required by law.

7. Are there risks to me in taking part in this study?

No questions will be asked of you about any specific instances or memories of your time in the ICU. However, it is possible that you may experience some discomfort or distress as you may recollect some unpleasant memories from your stay in intensive care. Participation in the study will ensure that distress can be potentially diagnosed and appropriate referral made. In the unlikely event that you do feel distressed by any of the questions, we would encourage you to discuss any concerns with the study coordinator or your General Practitioner.

8. Will I benefit from the study?

This study aims to look at the psychological impact of ICU stay and gain further medical knowledge. This study may help to improve treatment for others with similar conditions, and the results of the study will be published in a major international medical journal. You may not receive any direct benefits from this research.

9. Will taking part in this study cost me anything, and will I be paid?

Participation in this research study will not cost you anything. You will not be paid or receive any financial benefits from taking part in this research study.

10. What happens with the results?

The results obtained will be collated and published in medical journals, conference presentations and other professional forums. In any publication, information will be provided in such a way that you cannot be identified. Results of the study will be provided to you, if you wish.

11. What should I do if I want to discuss this study further before I decide?

When you have read this information, the study investigator will discuss it with you and clarify any queries you may have. If you would like to know more at any stage, please do not hesitate to contact _____ on _____, or study coordinator _____ on _____.

12. Who can I contact if I have any questions or problems?

For questions about the study you can contact the principal investigator, Dr _____ on _____or email _____. You may also contact the site research coordinator, _____ on _____ or email at _____

If you find that any of the research questions are distressing to you, please do not continue with the study. There are services to help you. Please talk to your GP, or contact one of the services below:

- Lifeline (24 Hours): 13 11 14 - www.lifeline.org.au
- ACT Health (Crisis Team): 1800 629 354 or (02) 6205 1065
- NSW Mental Health Line: 1800 011 511
- Beyond blue (24 Hours): 1300 224 636 - www.beyondblue.org.au
- SANE (9:00am - 5:00pm): 1800 187 263 - www.sane.org
- Suicide Callback Service (24 Hours): 1300 659 467 - www.suicidecallbackservice.org.au

13. Who should I contact if I have concerns about the conduct of this study?

This study has been approved by _____ Health Human Research and Ethics Committee. Any concerns or complaints about the conduct of this study can be directed to the _____ Health Directorate Human Research Ethics Committee Secretariat, on _____ or via email _____

Thank you for taking the time to consider this study.
If you wish to continue to take part in it, please sign the attached consent form.
This information sheet is for you to keep.

Appendix 2

FAMILY MEMBER/NEXT OF KIN INFORMATION SHEET

Psychological StRess in Intensive CarE Survivors (PRICE study)

Invitation

You are invited to participate in a research study being conducted by the _____ Hospital Intensive Care Unit (ICU) looking at the incidence of psychological symptoms in close family members of patients who have been admitted to the ICU. We will also study the incidence of psychological symptoms in intensive care patients.
Critically ill patients requiring support in ICU may take a minimum of 6-12 months to physically get back to what is normal for them. It has become apparent that ICU relatives are also traumatised by their ICU experience and can sometimes show high levels of psychological symptoms. This study is being conducted to look for the incidence of such symptoms.

1. What is the purpose of this study?

To screen families/next of kin of ICU patients for psychological symptoms after their stay in ICU. Participants in the study will be followed up to 12 months post discharge from ICU. This knowledge will assist in deepening understanding of the long term impact of ICU thus facilitating strategies, prevention and treatment of psychological symptoms.

2. Who is conducting this study?

The research team at the Intensive Care Unit of the _____ Hospital is conducting the study.

3. Why have I been invited to participate in this study?

You are the family member/next of kin (NOK) of a critically ill patient who is admitted to intensive care needing organ support This makes you eligible to participate in the study.

4. What if I don't want to take part in this study or if I want to withdraw later?

Participation in this study is voluntary and your decision will not affect the medical management of your loved one. If you wish to withdraw from the study, you can do so at any time without justifying your decision. If you do withdraw from the study, all of the data already collected about you as part of the study will be destroyed and no data or information collected will be used in anyway by the researchers or sent

outside this institution. No additional information will be collected for the purposes of this study and you will not be contacted again.

5. What does this study involve?

Participation in this study involves 3 short surveys after the discharge of your loved one from ICU. An initial survey will be done in hospital after ICU discharge. One of the research investigators will meet you while you are still in hospital. Follow up surveys will be done at 3 and 12 months after discharge. This will be in the form of either a postal or a telephonic interview answering a short series of questions. This will assist us to determine if there have been any changes during that time.
Families/next of kin will be responding to a Revised Impact of Event Scale (IES-R) & Depression Anxiety Score Scale-21 (DASS-21). These tools measure the level of distress you may be experiencing as a result of your loved one being admitted to intensive care. In addition, we would be assessing the impact of your family members' hospitalisation on your quality of life using a validated tool called EQ-5D

6. Will my taking part in this study be kept confidential?

You have the right to privacy and all information that is collected during this study is confidential to the extent permitted by the applicable laws and regulations. Your study data will be made anonymous by the assignment of a unique number to you alone. All data collected from you will then be identified by this number.
Paper records including contact information will be stored in locked rooms accessible only to authorized study personnel. Electronic information will be kept on password-protected computers accessible only to authorized study personnel.
Your identity will be kept confidential at all times. Your personal information will only be disclosed with your permission, except as required by law.

7. Are there risks to me in taking part in this study?

No questions will be asked of you about any specific instances or memories of the time your loved one was admitted in the ICU. However, it is possible that you may experience some discomfort or distress as you may recollect some unpleasant memories from that time. Participation in the study will ensure that distress can be potentially diagnosed and appropriate referral made. In the unlikely event that you do feel distressed by any of the questions, we would encourage you to discuss any concerns with the study coordinator or your General Practitioner.

8. Will I benefit from the study?

This study aims to look at the psychological impact of ICU stay and gain further medical knowledge. This study may help to improve support for others with similar experiences, and the results of the study will be published in a major international medical journal. You may not receive any direct benefits from this research.

9. Will taking part in this study cost me anything, and will I be paid?

Participation in this research study will not cost you anything. You will not be paid or receive any financial benefits from taking part in this research study.

10. What happens with the results?

The results obtained from de-identified data will be collated and published in medical journals, conference presentations and other professional forums. In any publication, information will be provided in such a way that you cannot be identified. Results of the study will be provided to you, if you wish.

11. What should I do if I want to discuss this study further before I decide?

When you have read this information, the study investigator will discuss it with you and clarify any queries you may have. If you would like to know more at any stage, please do not hesitate to contact _____ on _____, or study coordinator _____ on _____.

12. Who can I contact if I have any questions or problems?

For questions about the study you can contact the principal investigator, Dr _____ on _____ or email _____. You may also contact the site research coordinator, _____ on _____ or email at _____

If you find that any of the research questions are distressing to you, please do not continue with the study. There are services to help you. Please talk to your GP, or contact one of the services below:

- Lifeline (24 Hours): 13 11 14 - www.lifeline.org.au
- ACT Health (Crisis Team): 1800 629 354 or (02) 6205 1065
- NSW Mental Health Line: 1800 011 511
- Beyond blue (24 Hours): 1300 224 636 - www.beyondblue.org.au
- SANE (9:00am - 5:00pm): 1800 187 263 - www.sane.org
- Suicide Callback Service (24 Hours): 1300 659 467 - www.suicidecallbackservice.org.au

13. Who should I contact if I have concerns about the conduct of this study?

This study has been approved by _____ Health Human Research and Ethics Committee. Any concerns or complaints about the conduct of this study can be directed to the _____Health Directorate Human Research Ethics Committee Secretariat, on _____ or via email _____.

Thank you for taking the time to consider this study.
If you wish to continue to take part in it, please sign the attached consent form.
This information sheet is for you to keep.

Appendix 3

Psychological stRess in Intensive CarE survivors (PRICE Study)

Patient Consent Form

I, _____(Full name of patient) of _____(address), have been explained about the study and have been asked to consent to participate in a research project entitled: PRICE: Psychological stRess in Intensive CarE survivors

In relation to this study I have read the Patient Information Sheet and have been informed of the following points:

1. Approval has been given by the _____ Health Directorate Human Research Ethics Committee. The aim of the study is to investigate cognitive and psychosocial function of patients who are critically ill and mechanically ventilated in Intensive Care Unit (ICU).
2. The results obtained from the study will not be of direct benefit to my medical management.
3. The study procedure will involve an initial assessment immediately after ICU discharge and 2 follow up surveys up to 12 months after ICU discharge.
4. I consent to being surveyed via post/telephone/both (strike out which is not applicable), as explained in the Study Information Sheet.
5. Possible adverse effects or risks related to this study may include potentially experiencing discomfort as a result of reflecting on the experience in ICU. I am aware that in this case I will be offered psychological assistance.
6. I understand that I have the ability to withdraw consent and therefore participation in the study at any stage. I am also aware that this will not in any way jeopardise my present or future care, or my relationship with the hospital.
7. Should I develop a problem which I suspect may have resulted from my involvement in this project, I am aware that I may contact the study principal investigator, Dr _____ on _____ or email at _____.
8. Should I have any problems or queries about the way in which the study was conducted, and I do not feel comfortable contacting the study staff, I am aware that I may contact the _____ Health Directorate Human Research Ethics Committee Secretariat, on _____ or via email _____
9. Participation in this project will not result in any extra medical or hospital costs to either my partner/friend/relative or I.
10. I understand that while the results of the research will be made accessible, my involvement and the identity will not be revealed.

11. In giving my consent, I acknowledge that the relevant Health Department Officials and the staff directly involved in the study may examine my medical records only as they relate to this project.
12. There is no foreseeable injury as a result of participating in this study; therefore any compensation will not be applicable.

After considering all these points, I accept the invitation to participate in this study.

Name: _____Date: _____
Signature _____
Investigator (Name): _____Date: _____
Signature (Investigator) _____

REVOCATION OF CONSENT

PRICE: Psychological stRess in Intensive CarE survivors

I hereby wish to WITHDRAW my consent to participate in the study described above and understand that such withdrawal WILL NOT jeopardise any treatment or my relationship with my health care providers.

Signature Date

Please PRINT Name _____

Appendix 4

Psychological stRess in Intensive CarE survivors (PRICE Study)

Family members' consent form

I, _____(Full name) of _____(address), have been explained about the study and have been asked to consent to participate in a research project entitled: PRICE: Psychological stress in intensive care survivors

In relation to this study I have read the Information Sheet and have been informed of the following points:

1. Approval has been given by the _____ Health Directorate Human Research Ethics Committee. The aim of the study is to investigate the psychological effect of a stay in the ICU.
2. The results obtained from the study will not be of direct benefit to my loved one's medical management.
3. The study procedure will involve an initial assessment immediately after ICU discharge and 2 follow up surveys till 12 months.
4. I consent to being surveyed via post/telephone/both (strike out which is not applicable), as explained in the Study Information Sheet.
5. Possible adverse effects or risks related to this study may include potentially experiencing discomfort as a result of reflecting on the experience in ICU. I am aware that in this case I will be offered psychological assistance.
6. I understand that I have the ability to withdraw consent and therefore participation in the study at any stage. I am also aware that this will not in any way jeopardise the present or future care of my loved one, or my relationship with the hospital.
7. Should I develop a problem which I suspect may have resulted from my involvement in this project, I am aware that I may contact the study principal investigator, Dr _____ on _____ or email at _____.
8. Should I have any problems or queries about the way in which the study was conducted, and I do not feel comfortable contacting the study staff, I am aware that I may contact the _____Health Directorate Human Research Ethics Committee Secretariat, on _____ or via email _____.
9. Participation in this project will not result in any extra medical or hospital costs to either my partner/friend/relative or I.
10. I understand that while the results of the research will be made accessible, my involvement and the identity will not be revealed.

11. In giving my consent, I acknowledge that the relevant Health Department Officials and the staff directly involved in the study may examine my loved one's medical records only as they relate to this project.
12. There is no foreseeable injury as a result of participating in this study; therefore any compensation will not be applicable.

After considering all these points, I accept the invitation to participate in this study.

Name: _____Date: _____
Signature _____
Investigator (Name): _____Date: _____
Signature (Investigator) _____

REVOCATION OF CONSENT

PRICE: Psychological stress in intensive care survivors

I hereby wish to WITHDRAW my consent to participate in the study described above and understand that such withdrawal WILL NOT jeopardise any treatment of my loved one, or my relationship with my health care providers.

Signature Date

Please PRINT Name _____

Appendix 5

PTSS-14 Intensive Care Screen

This form should not take longer than about 5 minutes to complete. The form has two sections, Part A and Part B.

PART A

This consists of four statements about your memory of the time you spent on the Intensive Care Unit. Read each statement. If a statement is FALSE, tick the NO box. If the statement is TRUE, tick the YES box. Please answer ALL four questions. Tick only ONE box for each statement. If you make a mistake, simply cross out the wrong answer and tick the correct box.

PART B

This consists of 10 statements about how you have been feeling in the past few days. You need to decide HOW OFTEN you have been feeling this way in the past few days.

If you have NOT EVER felt or experienced what the statement says in the past few days, circle 1 (never).

If you have been feeling or experiencing it ALL THE TIME, circle 7 (always).

Otherwise, circle one of the numbers in between that best describes how much you have been feeling or experiencing what the statement says in the past few days.
Please circle only one number for each statement. If you make a mistake, simply cross it out and circle the correct number. PLEASE be sure to choose a number for ALL 14 statements.

A. When I think back to the time of my severe illness and the time I spent in the Intensive Care Unit (ICU), I remember:

Nightmares	No	☐	Yes	☐
Severe Anxiety or Panic	No	☐	Yes	☐
Severe Pain	No	☐	Yes	☐
Troubles to breath, feelings of suffocation	No	☐	Yes	☐

B. Presently (this means in the past few days) I suffer from:

1. sleep problems

never						always
1	2	3	4	5	6	7

2. nightmares

never						always
1	2	3	4	5	6	7

3. depression, I feel dejected/downtrodden

never always

1 2 3 4 5 6 7

4. jumpiness, I am easily frightened by sudden sounds or sudden movements

never always

1 2 3 4 5 6 7

5. the need to withdraw from others

never always

1 2 3 4 5 6 7

6. irritability, that is, I am easily agitated/annoyed and angry

never always

1 2 3 4 5 6 7

7. frequent mood swings

never always

1 2 3 4 5 6 7

8. a bad conscience, blame myself, have guilt feelings

never always

1 2 3 4 5 6 7

9. fear of places and situations, which remind me of the ICU

never always

1 2 3 4 5 6 7

10. muscular tension

never always

1 2 3 4 5 6 7

11. *upsetting, unwanted thoughts or images of my time on the ICU*

never always

1 2 3 4 5 6 7

12. *feeling numb (e.g. cannot cry, unable to have loving feelings)*

never always

1 2 3 4 5 6 7

13. *avoid places, people or situations that remind me of the ICU*

never always

1 2 3 4 5 6 7

14. feeling as if my plans or dreams for the future will not come true

never always

1 2 3 4 5 6 7

Citation: Twigg E, Humphris G, Jones C, Bramwell R, Griffiths RD. Use of a screening questionnaire for post-traumatic stress disorder (PTSD) on a sample of UK ICU patients. Acta Anaesthesiologica Scandinavica. 2008 Feb;52(2):202–8.

Appendix 6
IMPACT OF EVENT SCALE- REVISED

INSTRUCTIONS: Below is a list of difficulties people sometimes have after stressful life events. Please read each item, and then indicate how distressing each difficulty has been for you **DURING THE PAST SEVEN DAYS** with respect to _____, which occurred on _____. How much were you distressed or bothered by these difficulties?

Not at all = 0	A little bit = 1	Moderately = 2	Quite a bit = 3	Extremely = 4

1. Any reminder brought back feelings about it.
2. I had trouble staying asleep.
3. Other things kept making me think about it.
4. I felt irritable and angry.
5. I avoided letting myself get upset when I thought about it or was reminded of it.
6. I thought about it when I didn't mean to.
7. I felt as if it hadn't happened or wasn't real.
8. I stayed away from reminders of it.
9. Pictures about it popped into my mind.
10. I was jumpy and easily startled.
11. I tried not to think about it.
12. I was aware that I still had a lot of feelings about it, but I didn't deal with them.
13. My feelings about it were kind of numb.
14. I found myself acting or feeling like I was back at that time.
15. I had trouble falling asleep.
16. I had waves of strong feelings about it.
17. I tried to remove it from my memory.
18. I had trouble concentrating.
19. Reminders of it caused me to have physical reactions, such as sweating, trouble breathing, nausea, or a pounding heart.
20. I had dreams about it.
21. I felt watchful and on-guard.
22. I tried not to talk about it.

Citations: Weiss, D.S. & Marmar, C.R. (1997). The Impact of Event Scale-Revised. In J.P. Wilson, & T. M. Keane (Eds.), *Assessing Psychological Trauma and PTSD: A Practitioner's Handbook*. (pp. 399-411). New York: Guilford.

Weiss, D. S. (2004). The Impact of Event Scale-Revised. In J. P. Wilson, & T. M. Keane (Eds.), *Assessing psychological trauma and PTSD: A practitioner's handbook* (2nd ed., pp. 168-189). New York: Guilford Press.

Appendix 7

DASS21	*Name:*	*Date:*

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you *over the past week*. There are no right or wrong answers. Do not spend too much time on any statement.

The rating scale is as follows:
0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of time
3 Applied to me very much, or most of the time

1	I found it hard to wind down	0	1	2	3
2	I was aware of dryness of my mouth	0	1	2	3
3	I couldn't seem to experience any positive feeling at all	0	1	2	3
4	I experienced breathing difficulty (eg, excessively rapid breathing, breathlessness in the absence of physical exertion)	0	1	2	3
5	I found it difficult to work up the initiative to do things	0	1	2	3
6	I tended to over-react to situations	0	1	2	3
7	I experienced trembling (eg, in the hands)	0	1	2	3
8	I felt that I was using a lot of nervous energy	0	1	2	3
9	I was worried about situations in which I might panic and make a fool of myself	0	1	2	3
10	I felt that I had nothing to look forward to	0	1	2	3
11	I found myself getting agitated	0	1	2	3
12	I found it difficult to relax	0	1	2	3
13	I felt down-hearted and blue	0	1	2	3
14	I was intolerant of anything that kept me from getting on with what I was doing	0	1	2	3
15	I felt I was close to panic	0	1	2	3
16	I was unable to become enthusiastic about anything	0	1	2	3
17	I felt I wasn't worth much as a person	0	1	2	3
18	I felt that I was rather touchy	0	1	2	3
19	I was aware of the action of my heart in the absence of physical exertion (eg, sense of heart rate increase, heart missing a beat)	0	1	2	3
20	I felt scared without any good reason	0	1	2	3
21	I felt that life was meaningless	0	1	2	3

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation		Page no
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	√	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done	√	2
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	√	3
Objectives	3	State specific objectives, including any prespecified hypotheses	√	4
Methods				
Study design	4	Present key elements of study design early in the paper	√	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	√	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	√	4,5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	√	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	√	6
Bias	9	Describe any efforts to address potential sources of bias	√	Selection bias was minimised by record of a screening log, inclusion and exclusion criteria
Study size	10	Explain how the study size was arrived at	√	8

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	√	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	√	8.9
		(*b*) Describe any methods used to examine subgroups and interactions	√	9
		(*c*) Explain how missing data were addressed	N/A	
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A	
		(*e*) Describe any sensitivity analyses	√	9
Results			**N/A**	
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed		
		(b) Give reasons for non-participation at each stage		
		(c) Consider use of a flow diagram		
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders		
		(b) Indicate number of participants with missing data for each variable of interest		
		(c) Summarise follow-up time (eg, average and total amount)		
Outcome data	15*	Report numbers of outcome events or summary measures over time		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included		
		(*b*) Report category boundaries when continuous variables were categorized		
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		
Discussion			**N/A**	
Key results	18	Summarise key results with reference to study objectives		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence		
Generalisability	21	Discuss the generalisability (external validity) of the study results		
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	√	10

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.